filtered off and the filtrate was worked up in the usual way, and converted into its hydrochloride, yield 1.17 g.

N-(2-(4-Morpholinyl)ethyl)-2,4-dimethylbenzenesulfonamide (56).—To a solution of 2,4-dimethylbenzenesulfonamide (5.55 g, 0.03 mol) in 10% NaOH (30 ml) was added 2-morpholinoethyl chloride·HCl (5.52 g, 0.03 mol) and the mixture was refluxed for 3 hr. The mixture was cooled and extracted with Et_2O to remove unreacted morpholinoethyl chloride. The aqueous layer was acidified and extracted with EtOAc to remove unreacted dimethylbenzenesulfonamide. The acid layer was then basified to pH 7.5 and extracted with EtOAc, washed with H_2O, dried (Na_2SO_4), and the solvent was removed. The residual oil was converted into its hydrochloride, yield 4.8 g.

Acknowledgment.—We would like to convey our thanks to Dr. O. P. Babbar for the antiviral screening results, to Miss P. Sajnani for technical assistance, to Dr. U. K. Sheth and Riker Laboratories, Northridge, Calif. for making available the diuretic activity results, and to Riker Laboratories, Wellwyn Garden City, U. K. for some of the antifungal screening results.

1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocines. II[1-3]

NAOKATA YOKOYAMA, FRED B. BLOCK, AND FRANK H. CLARKE

Department of Medicinal Chemistry, Pharmaceuticals Division, Geigy Chemical Corporation, Ardsley, New York 10502

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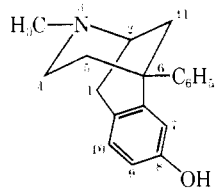
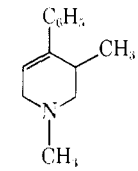
The synthesis of racemic 1,2,3,4,5,6-hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (VIII) and of its optical isomers is described. Evidence is presented for the assignment of the β configuration of the 11-methyl substituent. The *l* isomer is a potent analgetic with mild nalorphine-like antagonistic properties in mice.

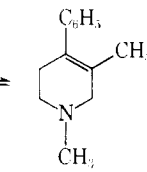
In the first paper of the series[1] the synthesis of 1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (I) was described. It was our hope that modification of the basic hexahydro-2,6-methano-3-benzazocine nucleus I would result in a more potent analgetic with interesting and advantageous properties. The synthetic scheme so successfully applied to the preparation of I again proved its value in the preparation of the corresponding compound with Me at C_{11}.[3]



I



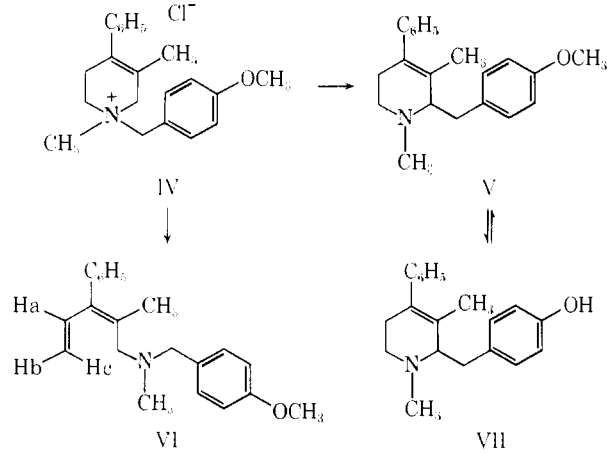
II



III

The required Δ^3-piperideine intermediate III was obtained by the procedure of Casy, *et al.*[4] These authors had prepared III by the acid-catalyzed dehydration of the *trans*-4-piperidinol obtained by the reaction of PhLi with 1,3-dimethyl-4-piperidone,[5] and found the dehydration product to be an equilibrated mixture of Δ^3- and Δ^4-piperideines.

Nmr spectral data showed that the initial dehydration product was an approximately equimolar mixture of II and III. Prolonged refluxing (48 hr) with HCl resulted in a mixture containing 85% of the required Δ^3-piperideine, III. The amount of III was estimated from the signal of the 3-Me substituent in the nmr spectrum of III in $CDCl_3$. It is interesting to note that this signal, which appeared as a triplet at δ 1.56 (J = 1.5 cps), is due to long range coupling with the CH_2 at the 5 position since it is found unchanged in the nmr spectrum of the 2-substituted derivative V.



IV V VI VII

Reaction of crude III with anisyl chloride in acetone gave the calculated yield of the desired crystalline quaternary ammonium salt IV and left the isomeric quaternary salt from the Δ^4-piperideine in solution.

The structure of IV was confirmed by its nmr spectrum in D_2O. The Stevens rearrangement[6] of IV to V proceeded in 65–75% yield (estimated by vpc) by stirring the dried quaternary salt IV and powdered KOH in refluxing toluene. For characterization, the crude 2-anisyl-Δ^3-piperideine derivative V was converted into the crystalline phenolic derivative, 2-(4-hydroxybenzyl)-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine VII, by short treatment with boiling 48% HBr. The pure Stevens base V was obtained from the phenol VII with CH_2N_2. The structures of the Stevens base V and of its corresponding phenol VII were confirmed by the nmr spectra. A minor product (about 5%) formed during the Stevens re-

(1) Part I. F. B. Block and F. H. Clarke, *J. Med. Chem.*, **12**, 845 (1969).

(2) Presented in part at the Symposium on Newer Analgetics and Narcotic Antagonists of the Medicinal Chemistry Section, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstract M-16.

(3) Chemical Abstracts nomenclature. Part I of this series,[1] footnote 3.

(4) A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, **23**, 1405 (1967).

(5) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(6) See ref 1 for a further discussion of this reaction in the 4-phenyl-Δ^3-piperideine series.

Table I

Substituent		Per cent of quaternization					
C_6	C_{11}	4 hr	5 hr	7 hr	8 hr	12 hr	24 hr
Me	H		82[a]		90.6[a]		98[a]
Et	H	79[a]			92[a]		98[a]
Pr	H	79[a]			91[a]		99[a]
(I) Ph	H	60	65	72			98
(IX) Me	α-Me	71[a]		83	85[a]		
Et	α-Et	52[a]		67	75[a]		
Me	α-Et	62[a]		75	80[a]		97[a]
(X) Me	β-Me	9.9[a]				24[a]	41[a]
Et	β-Et	2.3[a]				7[a]	12.5[a]
Me	β-Et				6.3[a]		16.[a]
(VIII) Ph	β-Me		3	4			11

[a] Data from ref 10.

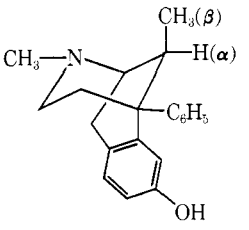
arrangement of IV was the Hofmann degradation product VI isolated as a crystalline HBr salt. The structure of VI was confirmed by ir, nmr, and uv spectra as well as elemental analysis.

The cyclization of the purified Stevens base VII with refluxing 48% HBr[7] for 48 hr gave the crystalline 6-phenyl-hexahydro-2,6-methano-3-benzazocine derivative VIII in 87% yield. The free base, mp 226–228°, was easily recrystallized from *i*-PrOH and formed a water-soluble HCl salt.

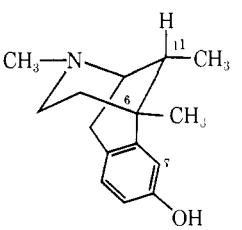
Resolution of the methanobenzazocine derivative VIII into its *d* and *l* optical isomers was achieved by fractional crystallization of the *d*-mandelate salts. The HCl salts of the resolved bases had rotations of +104° and −105°, respectively, in MeOH. The absolute configuration of the *l* isomer has been shown to correspond with that of morphine.[8]

Alternatively, optical resolution of the phenolic Stevens base VII was achieved by salt formation with optically active mandelic acids. Thus, the levorotatory base VII ($[\alpha]_D = -21°$) was regenerated following crystallization of its salt with *d*-mandelic acid from absolute EtOH. The corresponding dextrorotatory base ($[\alpha]_D = +26°$) was obtained in a similar manner using *l*-mandelic acid. The *d* base VIII was then obtained by cyclization of the *l* isomer of the Stevens base VII.

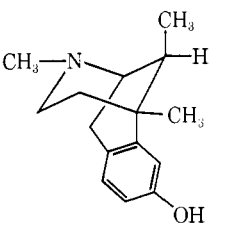
It was of interest to determine the configuration of the C_{11}-Me of VIII and to compare the result with that of the predominant isomer formed in the 6,11-dialkyl-methano-3-benzazocine series.[9] Fortunately, May and his associates have provided a useful and convenient method for the determination of configuration at the 11 position in the methano-3-benzazocine series.[10] By application of this method the relative configuration of the C_{11}-Me in VIII was determined by studying the rate of quaternization of VIII[11] with MeI in $CHCl_3$. The results were compared with those obtained with 11-desmethyl analog I[1] and a group of 6,11-dialkyl-2,6-methano-3-benzazocines[10-12] (Table I). From the



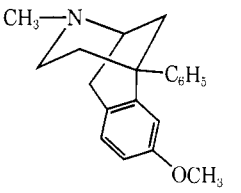
VIII



IX



X



XI

results it is apparent that the nature and size of the 6 substituent has very little effect on the rate of quaternization (see Table I). The effect on the rate of quaternization by 11α substituents in 6-alkyl-2,6-methano-3-benzazocines is also insignificant. However, 11β substituents, which have a 1,3-diaxial relationship to the lone pair electrons of the N atom, inhibit the rate by a factor of 5 to 25 times.[10] The 11-Me compound VIII was quaternized to the extent of only 4% in 7 hr while its desmethyl homolog I was converted into its quaternary salt under the same conditions to an extent of 72%. The results clearly indicate that the 11-Me in VIII has the β configuration as shown, and this conclusion has been confirmed by X-ray crystallography of the 4-bromobenzoyl ester of the *l* isomer of VIII.[8]

This result is surprising in view of the work of May and his associates who observed that cyclization of Stevens bases with HBr gave predominantly the 11α isomer in the corresponding 6,11-dialkyl series of 2,6-methano-3-benzazocines.[9] From an examination of models it appears that the 11-methyl substituent encounters less steric interactions on the α side of the C_{11} bridge in either 6-alkyl or 6-phenyl derivatives. We suggest that under the strongly acidic conditions required for the cyclization the more stable *trans* benzylcarbonium ion predominates during cyclization of the 4-phenyl-Δ^3-piperideine and this leads to the 11β-methyl isomer. On the other hand, in the case of the 4-alkyl-Δ^3-piperideine the carbonium ion lacks the stabilization of the phenyl nucleus and the cyclization of the 4-alkyl-Δ^3-piperideine may occur in a concerted

(7) Following the procedure of E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957), for the preparation of the corresponding 6-alkyl-2,6-methano-3-benzazocines.

(8) We are indebted to Dr. H. Jaggi of J. R. Geigy (Basel) for the determination of the crystal and molecular structure and the absolute configuration of the *p*-bromobenzoyl ester of *l*-VIII (personal communication). (For synthesis see Experimental Section).

(9) N. B. Eddy and E. L. May in "Synthetic Analgesics Part II A and B, Pergamon Press, Ltd., New York, N. Y., 1966, p 121.

(10) S. E. Fullerton, E. L. May, and E. D. Becker, *J. Org. Chem.*, **27**, 2144 (1962).

(11) The actual study was performed with the *d* isomer of VIII.

(12) We thank Dr. E. L. May, National Institutes of Health for a sample of α-1,2,3,4,5,6-hexahydro-3,6,11-trimethyl-2,6-methano-3-benzazocin-8-ol.

TABLE II

NMR SPECTRA[a] IN DMSO-d_6 AT 39°

	VIII	IX	X
11α-Me		0.83	
11β-Me	0.78		1.03
6-Me		1.23	1.20
7-H	5.77	6.60	6.69
9-H	6.48	6.48	6.48
10-H	6.89	6.87	6.85
N-Me	2.37	2.23	2.21

[a] Resonance is expressed in ppm downfield from the internal reference (TMS) signal.

manner to form the predominant 11α isomer of the product.[7]

An interesting observation has been made in a comparison of the nmr spectrum of VIII with those for the α- and β-6,11-dimethylmethanobenzazocines IX and X, respectively (see Table II). Although VIII possesses a β-orientated Me at C_{11} the signal due to this secondary C-Me appears in the same position as the corresponding signal of IX[10] rather than X. The explanation is apparent upon examination of the conformation of skeletal models of the respective compounds VIII, IX, and X. It is evident that the 11β-Me of VIII bears the same spatial relationship to the 6-phenyl ring as does the 11α-Me of IX to the aromatic ring of the methanobenzazocine skeleton. As a consequence, both methyls are shielded to a similar extent and their signals occur in the same position. This position is different from that of the signal of the 11β-Me in X. From these observations and the construction of space filling models[13] it appears that the plane of the 6-Ph of VIII is roughly perpendicular to the plane of the aromatic ring of the skeleton. Supporting evidence is seen in the X-ray analysis[8] and in the shielding effect of the 6-phenyl nucleus on the signal of the C_7-H in the nmr spectrum (Table II). The signal of the C_7-H of VIII is moved upfield from the corresponding signal in IX and X while signals of the C_9- and C_{10}-H are unaltered.

If the rotation of the 6-Ph is restricted, the shielding effect of the 6-Ph of VIII on the 11β-Me protons and C_7-H would be expected to decrease at elevated temperatures when the 6-Ph has more freedom to rotate. This prediction is borne out in Table III which summarizes the nmr data on C_{11}-Me, C_7-, C_9-, and C_{10}-H of VIII and XI at various temperatures.

A very small, but definite decrease of the shielding effect of the 6-Ph on the 11-Me and the C_7-H is observed at higher temperature with VIII as well as with XI.

As shown in Table IV, the new 6-phenylmethanobenzazocine derivative VIII proved to be more potent than morphine as an analgetic intraperitoneally in the hot plate test. The *l* isomer was about twice as potent as the racemate and the *d* isomer was about one-seventh as active. Neither the racemate nor the *d* isomer antagonized the analgetic effect of morphine in the tail-flick test.[14,15] The *l* isomer, however, partially antagonized (27%) the analgetic effect of morphine (10 mg/kg sc) at a dose of 0.5 mg/kg sc in the same test in mice.[15] In mice the LD_{50} of VIII and of its optical isomers were all in the range of 68 mg/kg ip and 185 mg/kg po.

Experimental Section[16]

1,3-Dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (III).—A mixture of *cis*- and *trans*-1,3-dimethyl-4-phenylpiperidin-4-ol was obtained from 506 g of 1,3-dimethyl-4-piperidone and 4.90 mol of PhLi in C_6H_6-Et_2O (Alfa Inorganics, Inc., Beverly, Mass.) according to the method described by Ziering and Lee.[5] The resulting piperidinol was extracted into HCl (2 l.) and refluxed. After 15 min at reflux temperature, dehydration was almost complete giving a mixture of the substituted 1,2,3,6- and 1,2,5,6-tetrahydropyridines (6:4 based on the nmr spectrum of the mixture).[4] Prolonged refluxing of the reaction mixture (48 hr) effected the conversion of most of the 1,2,3,6-tetrahydropyridine into the 1,2,5,6-tetrahydropyridine. At the end of this time, the reaction mixture was cooled in the ice bath, neutralized with NH_4OH, and extracted with Et_2O (3 × 1 l.). The Et_2O extract was washed (H_2O), dried (Na_2SO_4), and evaporated to dryness under reduced pressure, leaving an oil, 736 g. The crude product was distilled at 92–93° (1 mm) giving 625 g (85%) of a light yellow oil: nmr ($CDCl_3$) δ 1.57 (t, J = 1.5 cps, 3 H, vinylic C-Me), 2.37 (s, 3 H, N-Me), 2.2–3.2 (m, 6 H, ring CH_2), 7.1–7.5 (m, 5 H, aromatic protons); $n^{22}D$ 1.5486. The distillate was found to contain about 10% of 1,3-dimethyl-4-phenyl-1,2,3,6-tetrahydropyridine as determined by the nmr data in $CDCl_3$.

1-Anisyl-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridinium Chloride (IV).—A solution of 4.6 g of anisylchloride and 5.0 g of 1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine in 50 ml of Me_2CO was stirred at reflux for 2 hr during which time the pyridinium chloride formed as a crystalline precipitate. The reaction mixture was cooled to room temperature and the product collected by filtration, washed first with Me_2CO, then with hexane and dried in a vacuum oven to yield 8.07 g (87%) of white crystals, mp 184–187° (shrinkage at 180°). *Anal.* ($C_{21}H_{26}ClNO$) C, H, N, Cl.

TABLE III

	VIII				XI		
Temp, °C	C_{11}-Me[a]	C_7-H[b]	C_9-H[b]	C_{10}-H[b]	C_7-H[b]	C_9-H[b]	C_{10}-H[b]
39	0.78	5.77	6.48	6.89	6.00	6.64	7.04
70		5.78	6.46	6.88	6.02	6.65	7.04
80	0.79	5.79	6.46	6.88	6.04	6.66	7.04
130	0.82	5.83	6.47	6.89	6.13	6.68	7.04
150		5.85	6.48	6.89	6.15	6.68	7.04

[a] Resonance expressed in ppm relative to TMS. [b] Resonance determined with internal reference of benzene and expressed in ppm relative to TMS.

(13) The influence of N in these compounds is assumed to be small, see ref 10.

(14) Using a modification of the D'Amour-Smith technique: F. E. D'Amour and D. L. Smith, *J. Pharmacol.*, **72**, 74 (1941).

(15) Data from the Department of Pharmacology, Geigy Chemical Corp., Ardsley, N. Y.

(16) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. Melting points were determined on a Thomas–Hoover capillary melting point apparatus which has been calibrated with standard samples. Values of $[\alpha]D$ have been determined on a Perkin-Elmer 141 polarimeter and approximated to the nearest degree. Uv spectra were determined on a Beckman DB-G grating spectrophotometer. Ir spectra were determined on a Perkin-Elmer 137 NaCl spectrophotometer. The nmr spectra were determined on a Varian A/60 spectrometer in deuterated solvents (Me_4Si). Chemical shifts are recorded in δ values (ppm downfield from the reference signal). In nmr descriptions s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Vpc analyses were determined on an F and M 810.

A portion of the pyridinium chloride was converted into the H_2O-insoluble iodide by treatment with aq KI. Recrystallization from *i*-PrOH gave light yellow prisms, mp 173–174°. *Anal.* ($C_{21}H_{26}INO$), C, H, N, I.

Stevens Rearrangement of 1-Anisyl-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridinium Chloride (IV).—Compound IV (500 g) and powdered KOH (100 g) were suspended in 2.5 l. of PhMe. The use of C_6H_6 as solvent also gave the product but resulted in excessive foaming. The reaction mixture was stirred and refluxed for 16 hr while 37 ml of H_2O was collected in a Dean–Stark separator. The reaction mixture was cooled and filtered, and the filtrate was evaporated to dryness *in vacuo* leaving 440 g of a brown oil. Vpc data (5% Carbowax 20 *M*–Diatoport S60/80 column at 280°) on the oil indicated that the reaction product contained 65% of the desired *dl*-2-anisyl-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine. HCl and HBr salts of the reaction product resisted crystallization. (See the following Experimental Section for the description of the major reaction product). A minor reaction product VI was isolated in 5% yield as the HBr salt and recrystallized from *n*-BuOH, mp 219–220°: ir ν_{max}^{Nujol} 910 cm^{-1} (CH_2=CH); uv λ_{max}^{MeOH} 232 (ϵ 29,400), 279 mμ (sh, 1,340); nmr ($CDCl_3$) (the free base) δ 1.55 (s, 3, H, C-Me), 2.10 (s, 3 H, *N*-Me), 3.05 (s, 2 H, C_1-CH_2), 3.30 (s, 2 H, benzylic CH_2), 3.58 (s, 3 H *O*-Me); 4.35 (q, J_{ac} = 16 cps, vinylic proton H_c), 4.80 (q, J_{ab} = 11 cps, J_{bc} = 2 cps, vinylic proton H_b), 6.3–7.2 (m, 10 H, vinylic proton H_a and aromatic protons). *Anal.* ($C_{21}H_{26}BrNO$): C, H, N, Br.

***dl*-1,3-Dimethyl-2-(4-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine (VII).**—The crude 2-anisyl-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (7.5 g) was dissolved in 40 ml of 48% HBr. The solution was placed in an oil bath, preheated to 160°, and treated at reflux temperature for 15 min then cooled in an ice bath, neutralized with NH_4OH in ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated under diminished pressure leaving a foamy residue. The residue was crystallized from Et_2O to obtain 2.60 g (36%) of colorless crystals, mp 148–150°. Recrystallization from *i*-PrOH raised the melting point to 149.5–151°: nmr ($CDCl_3$) δ 1.51 (t, J = 1.5 cps, 3 H, vinylic C-Me), 2.0 ~ 3.35 (m, 7 H CH_2 and CH), 2.5 (s, 3 H, N-Me), 6.4–7.5 (m, 9 H, aromatic protons); λ_{max}^{MeOH} 229 (ϵ 16,300) 280 mμ (1850). *Anal.* ($C_{20}H_{23}NO$) C, H, N.

***dl*-2-Anisyl-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (V).**—Compound VII (2.93 g) was dissolved in 20 ml of MeOH and cooled in an ice bath. To the cooled solution was added a freshly prepared CH_2N_2 ethereal solution (70 ml of Et_2O solution from 10 g of *N*-methyl-*N*-nitro-*N*-nitrosoguanidine). The reaction mixture was allowed to stand at room temperature for 14 hr then evaporated to dryness leaving an oil. The crude product was dissolved in Et_2O and extracted into dilute HCl. The acidic layer was basified with KOH (pH 13) and extracted with Et_2O. The Et_2O extract was separated, washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo* to obtain 1.71 g (56%) of a yellow oil: nmr ($CDCl_3$) δ 1.50 (t, J = 1.5 cps, 3 H, vinylic C-Me), 2.40 (s, 3 H, *N*-Me), 2.0 ~ 3.3 (m, 7 H, CH_2 and CH), 3.67 (s, 3 H, *O*-Me); 6.7 ~ 7.4 δ (m, 9 H, aromatic protons).

***dl*-1,2,3,4,5,6-Hexahydro-3,11β-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (VIII).**—*dl*-1,3-Dimethyl-2-(4-hydroxybenzyl)-1,2,5,6-tetrahydropyridine (2.93 g) was dissolved in 75 ml of 48% HBr and the solution was refluxed for 18 hr. The reaction mixture was cooled in an ice bath, neutralized with NH_4OH in ice–water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated under reduced pressure leaving a foamy residue. The residue was treated with EtOAc to obtain 2.56 g (87%) of powder-like off-white crystals, mp 220–225°. Recrystallization from *i*-PrOH afforded colorless prisms, mp 226–228°: λ_{max}^{MeOH} 283.4 mμ (ϵ 11,800), λ_{min}^{MeOH} 250 (1900); nmr (DMSO-d_6) δ 0.78 (d, J = 7 cps, 3 H, C_{11}-Me), 2.37 (s, 3 H, *N*-Me), 1.2 ~ 3.5 (m, 8 H, CH_2 and CH), 5.77 (d, J_{7-9} = 2.5 cps, 1 H, C_7-H), 6.48 (q, J_{7-9} = 2.5 cps, J_{9-10} = 9 cps, 1 H, C_9-H), 6.8–7.5 (m, 6 H, other aromatic protons). *Anal.* ($C_{20}H_{23}NO$) C, H, N. The hydrochloride had mp 309–311° dec. *Anal.* ($C_{20}H_{24}ClNO$) C, H, N, Cl.

Optical Resolution of *dl*-2(4′-Hydroxybenzyl)-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine (VII). *d*-1,3-Dimethyl-2-(4′-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine *l*-Mandelate.—Compound VII (11.5 g) and *l*-mandelic acid (6.11 g) were dissolved in 200 ml of *i*-PrOH with heating and stirring. The solution was allowed to cool to room temperature to deposit prisms (9.0 g) mp 174–183°. The crystalline salt was recrystallized from absolute EtOH, yielding 7.2 g (41%) of colorless prisms, mp 185–196°, $[\alpha]^{28}D$ = −34° (*c* 1.77; l, 1 dm; MeOH). *Anal.* ($C_{28}H_{31}NO_4$): C, H, N.

***d*-1,3-Dimethyl-2-(4-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine Hydrochloride.**—The mandelate salt (5.4 g) was converted into the free base by treatment with NH_4OH and $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo* leaving an oil. The oil could be crystallized from hexane giving colorless prisms, mp 109–111° $[\alpha]^{28}D$ = +26° (*c* 1.06; l, 1 dm; MeOH). The free base was converted into the HCl salt with alcoholic HCl and crystallized from *i*-PrOH yielding 3.1 g (87%) of white crystals: mp 196–198°; $[\alpha]^{26}D$ = +10° (*c* 2.16; l, 1 dm; MeOH). *Anal.* ($C_{20}H_{24}ClNO$): C, H, Cl, N.

***l*-1,3-Dimethyl-2-(4-Hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine *d*-Mandelate.**—*dl*-1,3-Dimethyl-2-(4-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine (17.7 g) and *d*-mandelic acid (9.2 g) were dissolved in *i*-PrOH (300 ml) with heating. The solution after cooling to room temperature, deposited prisms, mp 170–188°, 14.0 g. The salt was recrystallized from EtOH to obtain 10.3 g (38%) of colorless prisms: mp 189–198°; $[\alpha]^{26}D$ = +36° (*c* 1.35; l, 1 dm; MeOH). *Anal.* ($C_{28}H_{31}NO_4$): C, H, N.

***l*-1,3-Dimethyl-2-(4-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine Hydrochloride.**—The mandelate salt (5.4 g) was converted into the free base by treatment with NH_4OH and $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo* leaving an oil. The oil could be crystallized from hexane: colorless prisms; mp 110–112°; $[\alpha]^{28}D$ = −21° (*c*, 1.12; l, 1 dm; MeOH). The free base was converted into the HCl salt with alcoholic HCl and crystallized from *i*-PrOH giving 3.2 g (90%) of white crystals, mp 196–198°. Recrystallization from MeOH raised the melting point to 197–198°; $[\alpha]^{27}D$ = −9° (*c* 2.36; l, 1 dm; MeOH). *Anal.* ($C_{20}H_{24}ClNO$); C, H, Cl, N.

Optical Resolution of *dl*-1,2,3,4,5,6-Hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (VIII). *l*-1,2,3,4,5,6-Hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol *d*-Mandelate.—To a warm solution of VIII (2.93 g) in absolute EtOH (100 ml) was added *d*-mandelic acid (1.52 g) with stirring and heating to give a clear solution. The solution, after standing at room temperature, deposited white needles, 1.78 g (40%), mp 223–227°. Recrystallization from absolute EtOH raised the melting point to 227–228°; $[\alpha]^{26}D$ = −38° (*c* 1.33; l, 1 dm; MeOH). *Anal.* ($C_{26}H_{31}NO_4$): C, H; N: Calcd 3.14, found, 3.65.

***l*-1,2,3,4,5,6-Hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol Hydrochloride.**—The mandelate salt (mp 227–228°) was treated with aqueous NH_4OH and Et_2O to liberate the free base. The Et_2O extract was washed (H_2O), dried (Na_2SO_4), and concentrated to a smaller volume to deposit colorless prisms, mp 198–199°; $[\alpha]^{28}D$ = −129° (*c* 1.59; l, 1 dm; MeOH). The free base was converted into its hydrochloride by treatment with alcoholic HCl in EtOH to give long colorless prisms: mp 312–315° dec; $[\alpha]^{25}D$ = −105° (*c* 1.19; l, 1 dm; MeOH). *Anal.* ($C_{20}H_{24}ClNO$): C, H, Cl, N. The methiodide, crystallized from MeOH, had mp 280–281° dec; $[\alpha]^{24}D$ = −76° (*c* 0.84; l, 1 dm; MeOH). *Anal.* ($C_{21}H_{26}INO$): C, H, I, N.

***d*-1,2,3,4,5,6-Hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol *d*-Mandelate.**—The mother liquor from the preparation of *l*-1,2,3,4,5,6-hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol *d*-mandelate (about 100 ml) (see the preceding experimental sections), was concentrated to about half its volume by heating at reflux and then allowed to stand at room temperature to deposit colorless prisms, 1.62 g (36%)

TABLE IV[a]

ANALGETIC ED_{50} VALUES IN MICE

Compound	Mg/kg sc
d,l-VIII	0.5
l-VIII	0.18
d-VIII	3.4
Morphine·HCl	1.2
Codeine·HCl	7.5
Meperidine·HCl	4.7

[a] We are indebted to Dr. E. L. May, National Institutes of Health for these values. The hot plate method and the values for standard compounds were reported by A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

mp 226–233°. Recrystalization of the crystals from absolute EtOH raised the melting point to 235–238°; $[\alpha]^{28}D = +118°$ (c 1.015; l, 1 dm; MeOH). *Anal.* ($C_{26}H_{31}NO_4$): C, H, N.

d-1,2,3,4,5,6-Hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol Hydrochloride.—The mandelate salt (mp 235–238°) was treated with NH_4OH and Et_2O to liberate the free base. The Et_2O extract was washed (H_2O), dried (Na_2SO_4), and concentrated to a smaller volume to yield colorless prisms: mp 197–198°; $[\alpha]^{28}D = +124°$ (c 1.50; l, 1 dm; MeOH). The free base was converted into its hydrochloride by treatment with alcoholic HCl in EtOH giving colorless needles: mp 310–312° dec; $[\alpha]^{28}D = +104°$ (c 1.26; l, 1 dm; MeOH). *Anal.* ($C_{20}H_{24}ClNO$): C, H, Cl, N.

Cyclization of l-1,2-Dimethyl-2-(4-hydroxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine. l-VII (13 g) was refluxed in 300 ml of 48% HBr for 48 hr. The reaction mixture was cooled in an ice bath, neutralized with concentrated NH_4OH in ice–water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated *in vacuo* yielding a residue which was crystallized from aqueous *i*-PrOH to obtain 11.7 g (90%) of white crystals: mp 196–198°; $[\alpha]^{25}D = +120°$ (c 1.46; l, 1 dm; MeOH). The melting point was not depressed upon admixture of the compound with *d*-VIII obtained from the *d*-mandelate salt.

dl-1,2,3,4,5,6-Hexahydro-8-methoxy-3-methyl-6-phenyl-2,6-methano-3-benzazocine Hydrochloride Hydrate.—To a suspension of *dl*-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol[1] (I, 5.0 g) in a 1:1 MeOH–$CHCl_3$ mixture (50 ml) was added freshly prepared 100 ml of CH_2N_2 ethereal solution (250 ml of solution from 20 g of nitrosomethylurea). The mixture was stirred at room temperature for 6 hr to obtain a clear solution, which was then evaporated *in vacuo* to an oil. The residue was treated with Et_2O (500 ml) and 1 *N* HCl (500 ml). The acidic layer was made alkaline (NH_4OH) and extracted with Et_2O (2 × 200 ml). The ethereal extract was washed (H_2O), dried (Na_2SO_4), and evaporated to leave a light yellow oil (5.4 g, 97%). The oil was dissolved in 0.5 *N* HCl (40 ml) with heating. The solution deposited fine prisms on cooling: 4.98 g (80%); mp 204–207° [dried at 80° (0.4 mm) for 6 hr]. *Anal.* ($C_{20}H_{24}ClNO \cdot H_2O$): C, H, Cl, N. The free base was prepared from the hydrochloride hydrate and used for the nmr study (see text).

l-8-(p-Bromobenzoxy)-1,2,3,4,5,6-hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocine.—A mixture of l-VIII (4.67 g) 4-bromobenzoyl chloride (12.10 g, Aldrich Chem., Milwaukee, Wis.) diisopropylethylamine (4.30 g Aldrich Chem., Milwaukee, Wis.) in 300 ml of C_6H_6 was refluxed on a steam bath for 2 hr, then, brought to dryness *in vacuo* to leave a residue. The residue was treated with $CHCl_3$ and aqueous $NaHCO_3$ solution. The $CHCl_3$ layer was separated, washed (H_2O), dried (Na_2SO_4), and evaporated to dryness to leave a white crystalline solid. The solid was crystallized from *i*-PrOH to obtain 22.0 g of colorless needles: 92%; mp 161–162°; $[\alpha]^{25}D = -65°$ (c 0.89; l, 1 dm; $CHCl_3$–MeOH (1:1)). *Anal.* ($C_{27}H_{26}BrNO_2$): C, H, Br, N. The compound was used for the X-ray crystallographic study (see ref 81).

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Linear Free Energy Relationships in the Alkaline Hydrolysis of Substituted Benzoylcholine Esters[1]

JAMES J. ZIMMERMAN[2] AND JERE E. GOYAN

University of California, School of Pharmacy, San Francisco, California 94122

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Rate constants have been determined for the alkaline hydrolysis of a series of *ortho*, *meta*, and *para* substituted benzoylcholine esters in 0.1 *M* aqueous NaCl at a constant pH of 7.4 and 37°. Substituent effects in the *meta* and *para* positions closely obey the Hammett equation and produce a ρ value of +1.540. The effects of substituents in the *ortho* position are accounted for by either a linear combination of σ_n^* and E_s^0 or by σ_I alone. A derivation is given to show that σ_I should be a linear function of σ_n^* and E_s^0. Interpretation of the substituent effects in the *ortho* position is most rationally based on σ_I in view of the incorrect assumptions made in defining σ_n^* and E_s^0. Substituent effects based on σ_I produce a ρ value of +2.088.

Substituent effect analysis has been successfully applied to an impressive number and variety of organic reactions, as documented by the compilations of Jaffé[3] and others.[4–6a] The success of these efforts in elucidating organic reaction mechanisms has been largely dependent on the comparisons made between the reaction rates of a new congeneric series of compounds and the substituent constants determined for an appropriate model process. The value of the reaction constant obtained from such a comparison provides a sensitive index of the susceptibility of the reaction center to the substituent effect and thus provides a means of comparing different reactions.

An examination of the reaction series for which ρ values have been determined reveals that relatively few series of biological substrates have been included in these analyses. In view of the current interest in utilizing physicochemical methods to explain drug activity, it would appear that the investigation of the purely chemical reactivity of congeneric series should be a fundamental part of many drug studies. Such an approach would provide a ρ value for the chemical reaction under the identical conditions of temperature and dielectric constant used in the biological assay and under

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(2) (a) To whom inquiries should be addressed: Temple University, School of Pharmacy, Philadelphia, Pa. 19140; (b) Trainee, National Institutes of Health Training Grant 5-T1-GM-726-03(1964–1968). American Foundation for Pharmaceutical Education Fellow (1966–1968).

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