TABLE I
ENZYMATIC HYDROLYSIS OF UNSUBSTITUTED P–N AMIDES

Compd	Formula	Reference, °C	μmol of NH_3/(mg) per 10 min
I[a]	$(HO)_2P(O)NH_2$	[b]	1.0
II	$(HO)P(O)(NH_2)_2$	[c]	11.8
III	$(EtO)_2P(O)NH_2$	[d]	0.0
IV	$[i\text{-PrO}]P(O)NH_2$	[d]	0.0
V	$(C_6H_5O)_2P(O)NH_2$	[e]	0.0
VI[f]	$(C_6H_5CH_2O)_2P(O)NH_2$	[d]	
VII[f]	$(C_6H_5NH)_2P(O)NH_2$	[g]	
VIII[h]	$C_6H_5OP(OH)NH_2$	[i]	0.0
IX	$C_6H_5NHP(O)(OH)NH_2$	[j]	0.0
X[k]	$C_6H_5CH_2OP(O)(OH)NH_2$	[k]	0.0
XI	$4\text{-}ClC_6H_4NHP(O)(OH)NH_2$	[l]	0.0
XII	$C_6H_5NHP(O)(OEt)NH_2$	[l]	0.0
XIII	$ClCH_2P(O)(NH_2)_2$	120–122[m]	3.1
XIV	$C_6H_5P(O)(NH_2)_2$	[n]	0.8
XV	$EtOP(NH_2)_2$	[o]	0.0
XVI	$(CH_3)_2NP(O)(NH_2)_2$	[n]	5.5
XVII	$CH_2{=}CHCH_2NHP(O)(NH_2)_2$	59–62 (85%)[m]	0.0
XVIII	$Et_2NP(O)(NH_2)_2$	[n]	1.9
XIX	$n\text{-}BuNHP(O)(NH_2)_2$	[n]	1.1
XX	$CH_3(CH_2)_5NHP(O)(NH_2)_2$	104–108 (95%)[m]	0.8
XXI	$CH_3(CH_2)_7NHP(O)(NH_2)_2$	106–110 (87%)[m]	0.0
XXII[f]	$CH_3(CH_2)_9NHP(O)(NH_2)_2$	110–113 (87%)[m]	
XXIII	$C_6H_{11}NHP(O)(NH_2)_2$	113–117 (96%)[m]	0.5
XXIV	$(CH_2)_4NP(O)(NH_2)_2$	150–152 (86%)[m]	0.0
XXV	$(CH_2)_5NP(O)(NH_2)_2$	[p]	0.5

[a] Na salt. [b] H. N. Stokes, *Amer. Chem. J.*, **15**, 198 (1893). [c] H. N. Stokes, *ibid.*, **16**, 124 (1894). [d] F. R. Atherton, H. T. Openshaw, and A. R. Todd, *J. Chem. Soc.*, 660 (1945). [e] F. Ephraim, *Chem. Ber.*, **44**, 631 (1911). [f] Precipitates upon addition to incubation mixture. [g] A. V. Kirsanov and L. P. Zhuravlova, *Zh. Obshch. Khim.*, **31**, 598 (1961); *Chem. Abstr.*, **55**, 25751 (1961). E. S. Levchenko and I. E. Sheinkman, *ibid.*, **34**, 1145 (1964); *Chem. Abstr.*, **61**, 1787 (1965). [h] Ba salt. [i] R. M. Caven, *J. Chem. Soc.*, **81**, 1562 (1902). [j] Li salt. [k] V. M. Clark and A. R. Todd, *ibid.*, 2030 (1950). [l] K. Rorig, *J. Amer. Chem. Soc.*, **71**, 3561 (1949). [m] See Experimental Section. [n] A. Michaelis, *Ann. Chem.*, **293**, 193 (1896). W. C. Smith and L. F. Audrieth, *J. Org. Chem.*, **22**, 265 (1957). [o] M. Goehring and K. Niedenzu, *Chem. Ber.*, **89**, 1768 (1956). [p] Farbenfabriken Bayer-A.-G., British Patent 830,800 (1961); *Chem. Abstr.*, **56**, 3329 (1962).

concentration was shown not to inhibit the enzyme, each incubation vessel also contained 20% propylene glycol as a solvent for all substrates except I, II, VIII, and X (H_2O). All determinations were made in duplicate. Only two substrates were investigated at one time with standardization against I each determination. Controls and samples were treated identically except that the enzyme preparation was added to the former after incubation and cooling. Enzyme activity was stopped by addition of an equal volume of cold 10% Cl_3CCO_2H. Vessels were maintained in an ice bath prior to, and after, incubation. VIII was treated with an equimolar amount of Na_2SO_4 prior to incubation. As a true control I was treated with sufficient $BaCl_2$ and Na_2SO_4 to yield a corresponding 0.012 *M* concentration of $BaSO_4$. Liberated NH_3 attributable to both chemical and enzymatic hydrolysis did not exceed 5% of theoretical with any substrate.

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The Synthesis of Pentazocine

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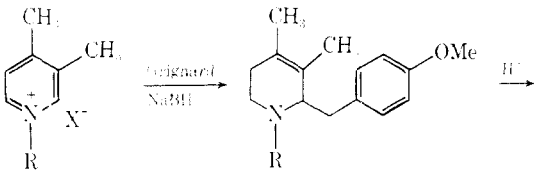
Although pentazocine (III, R = $CH_2CH{=}CMe_2$) is now commerically available, the route for its synthesis has not been described in the chemical literature[1] except for the brief statement that "our synthetic procedure does not give the *N*-methylbenzomorphan."[2]

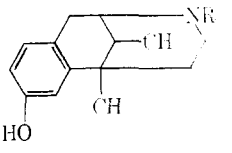
(1) Belgium Patent 719,408 covering the synthesis has been issued Feb 13, 1969.

(2) B. F. Tullar, *et al.*, *J. Med. Chem.*, **10**, 383 (1967).

The accompanying formulas where RX is MeI show May's original synthesis of 6,7-benzomorphans.[3] Demethylation of III, R = CH_3, to produce III, R = H, requires three steps. Our modification utilizes benzyl chloride for the quaternization of 3,4-lutidine. This affords a more favorable *cis:trans* isomer ratio in III,



I II



IIIa, R = CH_3
b, R = $C_6H_5CH_2$

and the *N*-benzyl group is removed in one operation. Alkylation of the resulting base completes the synthesis of pentazocine.

Kametani and coworkers recently described[4] essentially the same synthesis *via* the benzyl route, but

(3) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957); N. B. Eddy, J. G. Murphy, and E. L. May, *ibid.*, **22**, 1370 (1957).

(4) T. Kametani, K. Kigasawa, M. Hiiragi, T. Hayasaka, N. Wagatsuma, and K. Wakisaka, *J. Heterocycl. Chem.*, **6**, 43 (1969).

their experimental procedure differs from ours in the use of Ib as a hydrate for the Grignard reaction, and in their use of distillation and chromatography in the purification of II, whereas we achieved final purification of IIb through the direct formation of the oxalate salt.

Experimental Section[5]

1-Benzyl-3,4-dimethylpyridinium Chloride (Ib).—A solution of 42.2 g of $C_6H_5CH_2Cl$ and 35.7 g of 3,4-lutidine in 100 ml of Me_2CO was allowed to stand overnight at room temperature. The product, obtained in 81–89% yield in two crops, melted at 196–197.5°. *Anal.* ($C_{14}H_{16}ClN$) C, H, N.

1-Benzyl-2-(*p*-methoxybenzyl)-3,4-dimethyl-1,2,5,6-tetrahydropyridine (IIb).—The Grignard reagent from 36.3 g of *p*-methoxybenzyl chloride (using 3 l. of Et_2O/mole to reduce coupling) was added to 32.8 g of Ib in Et_2O. The mixture was stirred and refluxed for 1.5 hr and poured into a solution of 14 g of NH_4Cl in H_2O. Crude bianisyl was removed by filtration, the Et_2O layer separated and washed with H_2O, and the dihydropyridine isolated as a crude residue (57.5 g) by removal of the Et_2O. This was reduced in EtOH with 3.9 g of $NaBH_4$ in H_2O. The reaction mixture was stirred overnight at room temperature and the EtOH then removed *in vacuo*. The aqueous phase was extracted with Et_2O and the latter extracted in several portions with a total of 17.5 g of 85% H_3PO_4 in 400 ml of H_2O. Addition of excess 35% aqueous NaOH to the acid extracts, extraction of the resultant oil into Et_2O, drying, filtration, and concentration afforded 32.5 g of crude base. This was added to 9.1 g of oxalic acid in 100 ml of Me_2CO to precipitate 31.2 g of IIb·oxalate, mp 153–158°. *Anal.* ($C_{22}H_{27}NO \cdot C_2H_2O_4$) C, H, N.

3-Benzyl-1,2,3,4,5,6-hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol·HBr (IIIb).—A mixture of 53.8 g of crude IIb·oxalate, 145 ml of HOAc, and 285 ml of 62% HBr was refluxed for 22 hr, concentrated *in vacuo*, and diluted with 800 ml of *i*-PrOH. The slurry was stirred, concentrated to about 250 ml, cooled, and filtered. The product was taken up in EtOH and precipitated with about an equal volume of Et_2O to give 23.7 g of IIIb as the hydrobromide, mp 259–262°. *Anal.* ($C_{21}H_{25}NO \cdot HBr$) C, H, Br.

The *i*-PrOH mother liquors contain some of the *trans* isomer, mp 275–276° corrected. *Anal.* ($C_{21}H_{25}NO \cdot HBr$) C, H, N.

1,2,3,4,5,6-Hexahydro-*cis*-6,11-dimethyl-2,6-methano-3-benzazocin-8-ol (III, R = H).—Reduction of 11.8 g of IIIb·HBr in DMF using a 10% Pd–C catalyst gave, after removal of the catalyst and solvent and basification with NH_4OH, 6.0 g of product, mp 234–235°.[6] *Anal.* ($C_{14}H_{19}NO$) C, H, N.

Alkylation of this base with 1-bromo-3-methyl-2-butene to give pentazocine has been described.[7]

(5) Melting points are not corrected for emergent stem errors.

(6) E. M. Fry and E. L. May [*J. Org. Chem.*, **24**, 116 (1959)] report mp 232–235° corrected.

(7) S. Archer, N. F. Albertson, L. S. Harris, Anne K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).

Substituted Benzamides. Analogs of β-Hydroxyethylcyclohexylamine with CNS Depressant and Hypotensive Activity

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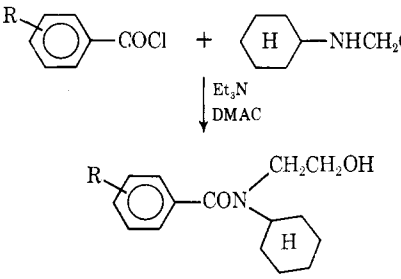
In a previous publication[1] we reported the synthesis and pharmacological evaluation of a series of ring-substituted *N*-(β-cyanoethyl)-*N'*-cyclohexylbenzamides. The biological activity of these compounds was studied in mice and rats for their effect on spontaneous motor activity and blood pressure. They were found to exert a depressant action on the spontaneous activity of mice at a dosage level of 4 mg/kg and effect a prolonged reduction in blood pressure of normotensive rats at this dosage. It was noted that the most active analogs studied were the *p*-chloro- and the *p*-methoxy-*N*-(β-cyanoethyl)-*N'*-cyclohexylbenzamides.

This paper reports a convenient synthesis and pharmacological evaluation for a series of amides of *ortho*-, *meta*-, and *para*-monosubstituted benzoic acids (**1**–**9**).



1, **2**, **3**, R = *p*-, *m*-, *o*-OCH_3
4, **5**, **6**, R = *p*-, *m*-, *o*-Cl
7, **8**, **9**, R = *p*-, *m*-, *o*-CH_3

Effects on the Central Nervous System of Mice. Gross Observation.—At a dose of 5 mg/kg, administered intraperitoneally (i.p.), **1**–**9** caused sedation without sleep in mice. A persistent state of tranquility developed within 10 min following administration and lasts for several hours. The animals' overall response pattern was similar to that observed with chlorpromazine with **1**, **3**, **4**, **5**, **7**, and **9**, demonstrating greater depressant activity. The test compounds potentiate the sedative action of reserpine.

Experimental Section[2]

General Method of Preparation of Amides.—Equimolecular amounts of the substituted benzoyl chloride and *N*-(β-hydroxyethyl)cyclohexylamine (Abbott Laboratories, North Chicago, Ill.) were dissolved in freshly distilled DMAC. The acyl halide solution was then added to a cooled, well-stirred mixture of the *N*-(β-hydroxyethyl)cyclohexylamine solution and Et_3N. When the addition of the acyl halide solution was completed, the crude substituted benzamide was precipitated by the addition of cold H_2O and collected. The crude product was recrystallized from EtOH–H_2O to give the pure compounds listed in Table I.

Pharmacologic Methodology. Gross Observations.—To study the *in vivo* effects, C3H mice weighing between 20 and 25 g were used. All test compounds were dissolved in propylene glycol and administered orally and i.p. Dose–response curves were obtained using 8 mice (rats) at each of four dose levels, and the median effective dose (ED_{50}) was calculated.

The effect of the compounds on reserpine-induced sedation was studied in mice by injecting them i.p. 4 hr following the administration of 2.5 mg/kg of reserpine i.p. and compared with that of the control groups at varying intervals.

Wistar rats dosed simultaneously with amphetamine (0.4%) 4 mg/kg i.p. and test compounds **1**, **3**, **4**, **7**, and **9** did not exhibit the characteristic symptoms (tremors, pacing, piloerection) noted in control animals receiving only the aforementioned dose of amphetamine.

Spontaneous Activity.—The depressant activity of the test compounds was determined in mice with actophotometers (Metro Industries, Inc., New York, N. Y.). The total body

(1) W. D. Roll, *J. Pharm. Sci.*, **57**, 1671 (1968).

(2) Melting points were determined using a Mettler FP-1 melting and boiling point apparatus and are corrected. Analyses (C, H) were obtained with a Coleman C-H analyzer, and where they are indicated only by symbols of the elements analytical data obtained for these elements were within ±0.4% of the theoretical values. Ir spectra were obtained with a Perkin-Elmer spectrophotometer Model 137-B (KBr).