1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocines. I. The 3-Carboxamido-8-hydroxy Derivative as an Orally Effective Analgetic[1]

FRED B. BLOCK AND FRANK H. CLARKE

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

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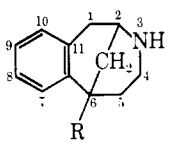
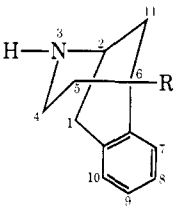
The synthesis of 3-carboxamido-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol (VII) is described. In a preliminary clinical trial VII has been shown to be an orally effective analgetic. This compound has an unusual freedom from toxicity in rats and dogs, and from physical dependence capacity in the monkey.

In the search for an analgetic free of unwanted side effects, May[2] and his associates have prepared derivatives of 6-alkyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (Ia and b).[3]



Ia



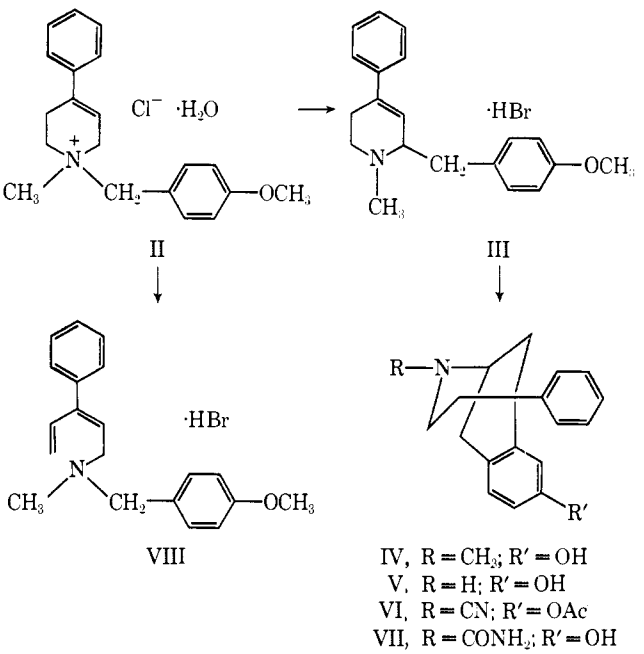
Ib

As has been noted by Walker and Alkalay,[4] similar derivatives with a 6-phenyl substituent have not been investigated adequately and it was our hope that they would provide orally effective analgetics free of the physical dependence capacity and psychotomimetic side effects associated with many of the 6-alkyl compounds and their antagonists.[5]

Our synthetic approach to the 6-phenyl-2,6-methano-3-benzazocines followed closely the path described by May and his associates[6] for the corresponding 6-alkyl derivatives. At the outset we planned to prepare derivatives with an 8-hydroxy substituent. Our starting material was the quaternary ammonium salt II which was readily obtained by treating 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine[7] with *p*-methoxybenzyl chloride[8] in acetone.

The preparation of the Stevens rearrangement product III was conveniently carried out by stirring the suspension of II and powdered KOH in refluxing benzene.[9] The HBr salt III was isolated in 75% yield (Scheme I). Apparently, a nonprotic solvent is important, since in ethanolic NaOEt Hofmann elimination occurred to give VIII as the major product.[10] Early experiments using PhLi as base in the manner described by May and his associates[6] gave the Stevens rearrangement product in lower yield.

SCHEME I



IV, R = CH_3; R′ = OH
V, R = H; R′ = OH
VI, R = CN; R′ = OAc
VII, R = $CONH_2$; R′ = OH

Cyclization of III with 48% HBr led to the desired 6-phenyl-2,6-methano-3-benzazocine derivative IV. The structures of III, the Hofmann degradation product VIII, and the methanobenzazocine IV were confirmed by their analyses and spectral properties (see Experimental Section). It is interesting to note that due to the shielding effect of the 6-phenyl substituent the 7-proton in the nmr spectrum of IV is moved upfield from the corresponding signal of the 9-proton. This phenomenon is discussed in greater detail in paper II of this series.[11]

Some of our studies required the availability of the nor base V as the key intermediate. In applying the conditions of the von Braun degradation, the O-acetyl derivative was first prepared and on treatment with CNBr in refluxing $CHCl_3$ the N-cyano derivative VI was formed. When VI was treated with aqueous HCl in the usual manner, the water-insoluble (5 mg/l.) nonbasic N-carboxamido derivative VII was obtained instead. However, the LAH reduction of VI yielded V.

(1) 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.

(2) N. B. Eddy and E. L. May in "Synthetic Analgesics, Part IIA and B," Pergamon Press Ltd., New York, N. Y., 1966, p 113.

(3) Although compounds of this ring system are also commonly known as 6,7-benzomorphans,[2] we prefer *Chemical Abstracts* nomenclature. For clarity the numbering of Ia is repeated in the conformational representation Ib.

(4) Since the appearance of patents describing our work [Netherlands Patent 6,414,820 (June 21, 1965); *Chem. Abstr.*, **64**, 12653e (1966)] G. Walker and D. Alkalay, *J. Org. Chem.*, **31**, 1905 (1966), have reported a different synthetic route to the 8-deoxy-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocine.

(5) Reference 2, p 138.

(6) Reference 2, pp 120–121.

(7) C. J. Schmidle and R. C. Mansfield, *J. Am. Chem. Soc.*, **78**, 425 (1956).

(8) *p*-Methoxybenzyl chloride is known to be unstable: D. Carroll, *Chem. Eng. News*, 40 (Aug 22, 1960).

(9) F. H. Clarke, G. B. Silverman, C. M. Watnick, and N. Sperber, *J. Org. Chem.*, **26**, 1126 (1961), found that powdered KOH in Me_2CO was an excellent catalyst for the Smiles rearrangement.

(10) We would like to thank Dr. N. Yokoyama for suggesting this structure.

(11) N. Yokoyama, F. B. Block, and F. H. Clarke, to be published.

As described below, VII proved to be of unusual interest and a more convenient route to its synthesis made use of alkaline H_2O_2 under the conditions of the Radziszewski reaction.[12] When the final steps of this reaction sequence were repeated using $^{14}CNBr$ labeled VII was easily obtained.

Although VII was inactive as an analgetic in the tail-flick test under the usual conditions[13] other tests for analgesia surprisingly gave a positive response. Thus, in the hot plate procedure[14] oral doses of 50 and 100 mg/kg in mice caused increases in latency of reaction of 100 and 217%, respectively. (An oral dose of 50 mg/kg of morphine caused a 200% increase in latency of reaction.) Protection from pain produced by Haffner's method[15] in rats gave dose-related increases in pain threshold of 12, 37, and 55%, respectively, for oral doses of 5, 10, and 20 mg/kg of VII. (The comparable results for the same doses of morphine were 24, 53, and 61%, respectively.) These results were unexpected since all of the well-known analgetics of the morphine and 2,6-methano-3-benzazocine type possess a basic nitrogen and analgetic activity has not been reported for the known nonbasic N-carbamoylnormorphine.[16]

Additional pharmacological experiments showed VII to be remarkably free of undesirable side effects. The low toxicity of VII, for instance, contrasts sharply with that of morphine. The acute intraperitoneal LD_{50} in mice is 480 mg/kg (solution in propylene glycol) and oral doses of up to 5000 mg/kg (suspension in 1% carboxymethylcellulose) failed to cause death. The animals showed some sensitivity to touch and a slight increase in spontaneous activity. Rats showed a similar lack of toxicity after oral administration of large doses of VII. In rabbits intravenous doses of 3–10 mg/kg of VII (in propylene glycol) caused no effect on respiration in contrast to morphine which, at 3 mg/kg depressed respiration by 60–70%. In 28-day subchronic studies in rats and dogs in which doses of up to 140 mg/kg/day of VII were administered orally there was no significant toxicity.

Furthermore, VII failed to show typical morphine-like withdrawal symptoms following chronic administration to monkeys.[17] Nalorphine (10 mg/kg sc) was administered to mice after treatment for 3 days with a total of 15 doses (cumulative dose 4.4 g/kg *po*) of morphine or VII. The morphine-treated mice showed severe withdrawal symptoms including seizures, lacrimation, salivation, tremors, vocalization, and hypermotility. Nalorphine produced no effect on the behavior of mice treated with VII. When animals stabilized on morphine (2 mg/kg every 6 hr) were given 200 mg/kg of VII orally every 4 hr for 20 hr instead of their regular morphine doses, VII failed to substitute. Also, 5 mg/kg of VII administered subcutaneously 14 hr after abrupt withdrawal of morphine from stabilized animals failed to suppress the abstinence phenomena.[17]

Compound VII has a very low solubility in H_2O (about 5 mg/l.). Nevertheless, experiments performed in rats using the Levine technique[18] with VII labeled with ^{14}C in the carboxamido group indicate that VII is completely absorbed from the rat intestine within 3 hr when administered as a solution in propylene glycol and to the extent of 21% in 3 hr when given as a suspension in 1% carboxymethylcellulose.

Finally, in a preliminary clinical trial, the analgetic effectiveness of VII was confirmed. In a double blind study involving 156 patients with moderate or severe postoperative fracture or somatic pain an oral dose of 40 mg of VII was essentially as effective as an oral dose of 60 mg of codeine. Both drugs were significantly superior to placebo in this study.[19]

Experimental Section[20]

1-Methyl-1-(*p*-methoxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridinium Chloride Monohydrate (II).—To a solution of 68.73 g (0.396 mole) of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine[3] in 200 ml of Me_2CO contained in a resin flask was added 78 g (0.50 mole) of *p*-methoxybenzyl chloride[8] in 200 ml of Me_2CO with constant stirring. The mixture was refluxed for 2 hr, cooled, and filtered. The colorless crystalline material was well triturated with Me_2CO and dried at 60° (15 mm) to yield 95% of II, mp 119–125°. A Karl-Fischer determination showed the presence of 5.83% H_2O. This material was used as such for the preparation of III. A 25-g sample of II was recrystallized from 125 ml of 1:2:2 *i*-PrOH–Me_2CO–Et_2O to give 22 g, mp 128–131°. *Anal.* ($C_{20}H_{24}ClNO \cdot H_2O$) C, H, Cl; H_2O: calcd, 5.17; found, 5.83, 6.02.

1-Methyl-2-(*p*-methoxybenzyl)-4-phenyl-1,2,5,6-tetrahydropyridine Hydrobromide (III). A. Using KOH.—A mixture of 142.0 g (0.43 mole) of II and 31.6 g of powdered reagent 85% KOH (ground in a ball mill for 24 hr) in 550 ml of C_6H_6 was refluxed for 5 hr under N_2. During this time, H_2O was continuously collected in a Dean–Stark separator. After 5 hr, 19.0 ml of H_2O was collected and an additional 0.7 ml was obtained after 19 hr of additional heating (expected, 21.8 ml of H_2O; 8.3 ml from II, 5.7 ml from KOH, and 7.8 ml from the Stevens rearrangement reaction). The solids were removed by filtration and the filtrate was treated with 39.6 ml of 47% HBr (80% of the theoretical amount). The mixture was refluxed until all the H_2O was collected as before. On cooling, there was isolated after drying at 60° (15 mm) 121 g (75%) of III, mp 163–166°. This material was used as such and converted to IV. Material recrystallized from *i*-PrOH melted at 167–169°; nmr ($CDCl_3$), δ 7.25 (d, J = 8.5 cps, ArH *meta* to OCH_3), 5.78 (m, vinyl H), 6.85 (d, J = 8.5 cps, ArH *ortho* to OCH_3), 3.76 (s, MeO). *Anal.* ($C_{20}H_{23}NO \cdot HBr$) C, H, Br.

B. Using PhLi.—To 19.77 g (0.060 mole) of finely ground II in 100 ml of anhydrous Et_2O was slowly added 33 ml of 2.00 *N* (0.066 mole) of PhLi (Lithium Corp. of America, New York, N. Y.). The yellow suspension was refluxed with rapid stirring for 2 hr. The cooled mixture was poured into 150 ml of ice and H_2O and the Et_2O phase was extracted with 10% HCl (three 80-ml portions). The aqueous phase was made basic with NH_4OH and extracted with Et_2O (three 70-ml portions). The Et_2O phase was washed (H_2O, 50 ml), dried ($MgSO_4$), and evaporated to yield 9.07 g of an oil. The oil dissolved in 50 ml of Me_2CO was treated with HBr gas until acid to congo red. After cooling and scratching there was isolated 3.44 g (15%) of III, mp 171–175°. The material was recrystallized from 100 ml of 1:1 EtOH–Et_2O (or *i*-PrOH) to give 2.97 g of III, mp 166–169°. Yields of 40% were obtained when 2.25 *M* equiv of PhLi was used in the same manner as described above.

(12) B. Radziszewski, *Ber.*, **17**, 1289 (1884).

(13) Modified D'Amour-Smith procedure: F. E. D'Amour and D. L. Smith, *J. Pharm. Exptl. Therap.*, **72**, 74 (1941).

(14) N. B. Eddy and D. Leimbach, *ibid.*, **107**, 385 (1953).

(15) C. Cianchi and J. Franceschini, *Brit. J. Pharm.*, **9**, 280 (1954).

(16) St. Weil and St. Rozenblumowna, *Roczniki Chem.*, **14**, 1309 (1934).

(17) G. Deneau and M. H. Seevers, Department of Pharmacology, School of Medicine, University of Michigan, Ann Arbor, Mich., personal communication.

(18) R. R. Levine and E. W. Pelikan, *J. Pharmacol. Exptl. Therap.*, **131**, 319 (1961).

(19) A. Sunshine, Knickerbocker Hospital, New York, N. Y., personal communication.

(20) Melting points (Thomas–Hoover capillary melting point apparatus) are corrected. The nmr data (δ) were obtained with a Varian A-60 spectrometer (TMS). All compounds were analyzed by nmr spectroscopy and the results confirm the assigned structures. In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet. Ir spectra were obtained with a Perkin-Elmer 137 NaCl spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

C. **Using BuLi.**—To a suspension of 20.0 g (60.8 mmoles) of II in Et_2O was slowly added under N_2, 87.5 mmoles of BuLi in hexane (Foote Mineral Co., New Johnsville, Penn.). The mixture was then refluxed for 2 hr, cooled, and poured into cold H_2O. The Et_2O phase was separated and extracted with four 50-ml portions of 2 *N* HCl. The aqueous extracts together with the H_2O–Et_2O-insoluble oil were rendered alkaline with NH_4OH. The precipitated base was taken up in Et_2O and the solution was dried ($MgSO_4$) before concentrating *in vacuo* to yield 11.32 g of an oil. The oil dissolved in Me_2CO was cautiously treated with HBr while cooling to yield 6.82 g (30%) of III, mp 168–171°.

5-[N-(4-Methoxybenzyl)-N-methyl]amino-3-phenyl-1,4-pentadiene Hydrobromide (VIII).—A mixture of 20.0 g of II and 150 ml of 1 *N* NaOEt in absolute EtOH was stirred and refluxed for 2 hr. The solvent was removed *in vacuo* and the residue was taken up in H_2O and Et_2O. The organic phase was separated, dried (Na_2SO_4), and evaporated to give 15.6 g (70% yield) of an oil. The base was converted to the HBr salt in anhydrous Et_2O, and recrystallized from Me_2CO; mp 198–199°; nmr ($CDCl_3$), δ 4.36 (s, benzyl H), 4.05 (d, NCH_2), 5.98 (t, $CH_2CH{=}C$), 5.42 (d, J = 11.5 cps, *cis*-$CH{=}CH_2$), 5.18 (d, J = 17 cps, *trans*-$CH{=}CH_2$), 6.80 (q, $CH{=}CH_2$), 6.88 (d, J = 8.5 cps, ArH *ortho* to OCH_3), 7.64 (d, J = 8.5 cps, ArH *meta* to OCH_3). *Anal.* ($C_{20}H_{23}NO \cdot HBr$) C, H, N.

1,2,3,4,5,6-Hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (IV).—A solution of 9.1 g (24.4 mmoles) of III in 91 ml of 48% HBr was refluxed for 24 hr. The solution was poured into 150 g of crushed ice containing excess NH_4OH and the solid was isolated by filtration to give 4.86 g (71%) of IV, mp 247–252°. In subsequent experiments, yields ranging to 87% were realized while the reflux period was shortened to 4 hr. Recrystallization from MeOH was accomplished by dissolving IV (3.26 g required 600 ml of MeOH) into a minimum of MeOH and concentrating to one-third its original volume; mp 249–252°; nmr (CF_3CO_2D), δ 7.19 (d, J = 8 cps, ArH, 10), 6.84 (q, J = 10 and 3 cps, ArH, 9), 6.22 (d, J = 3 cps, ArH, 7). *Anal.* ($C_{19}H_{21}NO$) C, H, N.

The **HCl salt** crystallized from Et_2O–MeOH; mp 294–296°. *Anal.* ($C_{19}H_{21}NO \cdot HCl$) C, H, Cl.

8-Acetoxy-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocine (IV-O-Acetate).—A mixture of 1.68 g (6.0 mmoles) of IV and 8.4 ml of Ac_2O was maintained at 100° for 45 min. The solution was poured into 20 ml of cold H_2O and after 5 min, 50% KOH in slight excess (ice-cooling) was added, and the liberated base was shaken quickly into Et_2O. The dried Et_2O solution was concentrated to yield 1.73 g (90%) of the desired compound. Recrystallization from *i*-Pr_2O or EtOAc gave 1.19 g (62%), mp 120–122°. *Anal.* ($C_{21}H_{23}NO_2$) C, H, N.

8-Acetoxy-3-cyano-1,2,3,4,5,6-hexahydro-6-phenyl-2,6-methano-3-benzazocine (VI).—To a solution of 2.59 g (24.4 mmoles) of CNBr in 30 ml of $CHCl_3$ was added 6.53 g (20.3 mmoles) of 8-acetoxy-1,2,3,4,5,6-hexahydro-3-methyl-2,6-methano-3-benzazocine over 0.75 hr. The solution was refluxed for 3 hr and the solvent was removed *in vacuo*. The residue was crystallized from Me_2CO or EtOH to yield 5.0 g (60%): mp 207–209°; ν_{max}^{Nujol} 2200, 1760 cm^{-1}. *Anal.* ($C_{21}H_{20}N_2O_2$) C, H, N.

1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocin-8-ol (V).—To a suspension of 5.60 g of LAH in 100 ml of dry THF under anhydrous conditions was added 5.0 g of VI dissolved by heating in 100 ml of dry THF. The mixture was refluxed for 17 hr and then decomposed with 29 ml of saturated NaCl solution. The mixture was refluxed for 1 hr and the filtrate was concentrated *in vacuo*. The residue was recrystallized from *i*-PrOH to yield 2.73 g, 69% of V, mp 239–241°. *Anal.* ($C_{18}H_{19}NO$) C, H, N.

3-Carboxamido-1,2,3,4,5,6-hexahydro-6-phenyl-2,6-methano-3-benzazocin-8-ol (VII).—To a mixture of 9.0 g of VI, 9.7 ml of 30% H_2O_2, and 30 ml of EtOH was added slowly 5.6 ml of 6 *N* NaOH with stirring and external cooling, while maintaining the pH at 8.5–9.0 and temperature at 35–40°. When addition was complete, the cooling bath was removed and the mixture was stirred at 50–60° for 3.5 hr. The pH of the mixture was adjusted to 5, the mixture was cooled and the solid was collected and washed (H_2O, EtOH) to yield 5.1 g (56%) of VII, mp 286–291°. Recrystallization from large volumes of MeOH raised the melting point to 292–294°. A preferred recrystallization solvent was DMSO–Me_2CO–H_2O (1:1:1); nmr (DMSO-d_6), δ 5.95 (s, NH_2); ν_{max}^{Nujol} 1565 (s), 1630 cm^{-1} (m). *Anal.* ($C_{19}H_{20}N_2O_2$) C, H, N.

Alternatively, VII was prepared by adding 8-acetoxy-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocine (1.92 g) in 30 ml of $CHCl_3$ to 0.76 g of CNBr in 15 ml of CHCl over 0.5 hr with stirring. The solution was refluxed for 3 hr and then evaporated to dryness *in vacuo*. The residue was refluxed in 25 ml of 6% HCl for 10 hr. The mixture was filtered hot and the solid was collected (1.46 g, mp 271–278°), dissolved in a minimum of MeOH, and concentrated to one-third its original volume. The solid which crystallized was collected and dried to yield 0.65 g (41%) of VII, mp 288–290°.

3-Carboxamido(^{14}C)-1,2,3,4,5,6-hexahydro-6-phenyl-2,6-methano-3-benzazocin-8-ol.—To a solution of 16.9 mmoles of $^{14}CNBr$[21] in 36 ml of $CHCl_3$ at 0° was added 4.50 g of 8-acetoxy-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocine dissolved in 50 ml of $CHCl_3$ during 45 min. The solution was then refluxed for 3 hr. After removal of solvent there was isolated a quantitative yield of 8-acetoxy-3-cyano(^{14}C)-1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocine, mp 189–195°. The radioactive material on treatment with 6% H_2O_2 at pH 8.5–9.0 in the manner described above yielded 2.98 g (69%) of 3-carboxamido(^{14}C)-1,2,3,4,5,6-hexahydro-6-phenyl-2,6-methano-3-benzazocin-8-ol, mp 275–278°. The two recrystallizations from 45 ml of 1:1:1 DMSO–Me_2CO–H_2O gave 2.10 g (49%), mp 286–287° of ^{14}C-VII.

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(21) A. Murray and D. Williams III in "Organic Syntheses with Isotopes, Part I," Interscience Publishers, Inc., New York, N. Y., 1958, p 589.