Structure and Biological Activity of Some Reduction Products of Strychnine, Brucine, and Their Congeners

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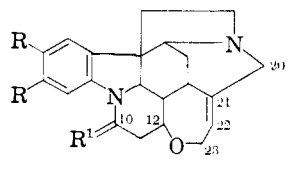
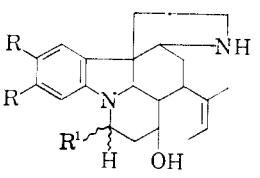
Reduction of strychnine, strychnidine, brucine, and brucidine with Na and methanol and ethanol in liquid ammonia cleaves the allylic ether linkage at C_{23}. Depending upon the conditions, the 21,22-olefinic bond may escape reduction, or concomitantly undergo partial or complete saturation. With strychnine and brucine these reactions are accompanied by conversion of the C_{10}-carbonyl to a secondary hydroxyl group. The seco derivatives XI, XII, and XIV, formed by reductive fission and saturation of the 21,22-bond, are potent antidepressant agents in experimental animals at doses showing no strychnine-like convulsant activity.

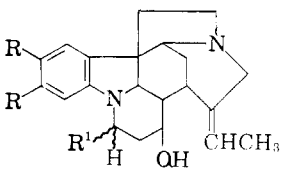
Clemo and King[2] have reported that strychnine (I) and strychnidine (II) were converted by Na and ethanol in liquid ammonia into amines which were formulated as the bis-seco derivatives V and VI, respectively. Such structures would result from concomitant fission of the C–O and C–N bonds involving the allylic 23 and 20 positions, and, while many similar scissions of allylic ethers have been observed,[3] to our knowledge no related metal–ammonia cleavages of allylic amines have been reported elsewhere in the literature; indeed, N-allyl and methallyl piperidines are converted by Na and methanol in liquid ammonia to the corresponding saturated amines without undergoing detectable fission.[4] This paper records a reinvestigation of the initial reductions, their extension to brucine and brucidine, and the results of biological testing of several of the products.



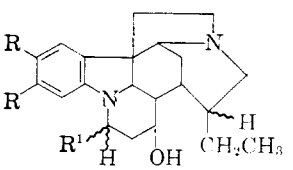
I, R = H; R¹ = O
II, R = H; R¹ = H₂
III, R = CH₃O; R¹ = O
IV, R = CH₃O; R¹ = H₂



V, R = H; R¹ = OH
VI, R = R¹ = H



VII, R = H; R¹ = OH
VIII, R = R¹ = H
IX, R = CH₃O; R¹ = OH
X, R = CH₃O; R¹ = H



XI, R = H; R¹ = OH
XII, R = R¹ = H
XIII, R = CH₃O; R¹ = OH
XIV, R = CH₃O; R¹ = H

Reduction of strychnine under Clemo and King's conditions gave a product, mp 164–166°, agreeing closely with the literature value of 165°,[2] which showed an accurate analysis for the molecular formula $C_{21}H_{28}N_2O_2$ as required by structure V. The substance exhibited typically indoline ultraviolet absorption and hydroxyl but no amide infrared absorption and was resolved by thin layer chromatography into two main components with a trace of a third. Now, reduction of I to V can, theoretically, give four distinct stereoisomers varying in the configuration of the C_{10}-hydroxyl and the gemometrical relationship of the C_{22}–C_{23}-ethylidene group with remainder of the polycyclic skeleton, so that the formation of three products seemed unexceptionable. However, structures of type V were excluded by the pmr spectrum which, while showing an expected one-proton signal ascribable to the carbinolamine proton at C_{10}, displayed high-field signals typical of C-methyl protons totalling only 2.9 protons in strength. These signal strengths were estimated by relating a series of multiplets in the aromatic region to the four protons at C_1–C_4 (see Table I which presents spectral data on the substrate and product in this and the other reductions described herein). The C-methyl resonances comprised a triplet 2.4 protons strong, and a doublet approximately 0.5 proton strong, associable, respectively, with the methyl protons in an ethyl group and a group of the ethylidenecycloalkyl type. The vinylic proton signal required for the ethylidene group was also displayed in the correct multiplicity and strength. Repetition of the reduction on a larger scale (see Experimental Section) gave a related product of lower melting point (158–162°) and higher optical rotation with elemental analysis corresponding to the molecular formula $C_{21}H_{26}N_2O_2$. This substance was resolved by thin layer chromatography into one principal and one trace component, the former having the same R_f as the minor of the two main components from the small-scale reduction. That it contained an ethylidene group of the ethylidenecycloalkyl type was demonstrated by the pmr spectrum which showed the required methyl doublet, now three protons strong, and the associated one-proton vinylic proton quartet. Also present was the expected one-proton multiplet attributable to the carbinolamine C_{10} proton. The foregoing data are satisfactorily interpreted by assigning the methyl and vinylic proton signals to the C_{23} and C_{22} protons, respectively, in structures of types VII and XI which would be formed by fission of C–O bonds only. Accordingly, the first reduction product can be defined as a mixture of structures of types VII and XI, and the second as a mixture of structures of type VII. Although VII and XI can each exist as four stereoisomers, each constituent appears to travel as one component in thin layer chromatography. The partial reduction of the Δ^{21} bond may possibly be due to the initial formation, by typical allylic C–O fission with double-bond

(1) Postal address: P. O. Box 8299, Philadelphia, Pa. 19101.
(2) G. R. Clemo and T. J. King, *J. Chem. Soc.*, 1661 (1948).
(3) H. Smith, "Organic Reactions in Liquid Ammonia," Interscience Publishers, Inc., New York, N. Y., 1963, p 162, and references there cited.
(4) T. J. King, *J. Chem. Soc.*, 898 (1951).

TABLE I: PMR DATA[a] AND LIGHT ABSORPTION DATA[b] FOR STRYCHNINE, BRUCINE, AND THEIR DERIVATIVES

Compd	Proton resonances							Acetate	Light Absorption	
	C$_7$–C$_4$	C$_{22}$	C$_{12}$	C$_{10}$	Methoxyl	C$_{23}$[e]	C$_{23}$[d]	CH$_3$	λ_{max}, mμ	Log ε
Strychnine I[g]	7.0–8.1 (m, 4)	5.89 (t, 1, 6.5)							254, 278, 288	4.11, 3.62, 3.42[f]
Strychnidine II	6.2–7.4 (m, 4)	5.82 (t, 1, 6.5)							256, 306	3.95, 3.43[g]
Brucine III[h]	7.78 (s, 1), 6.78 (s, 1)	5.84 (t, 1, 6.5)			3.85 (s, 3), 3.82 (s, 3)				263.5, 300.5	4.09, 3.93[i]
Brucidine IV	6.58 (s, 1), 6.03 (s, 1)	5.70 (t, 1, 6.5)			3.79 (s, 3), 3.76 (s, 3)				258, 321	3.97, 3.77
VII	6.4–7.4 (m, 4)	5.56 (q, 1, 6.5)		5.31 (m, 1)		1.70 (d, 3, 6.5)			253, 305	4.07, 3.48
VII + XI	6.4–7.4 (m, 4)	5.56 (q, 0.2, 6.5)		5.31 (m, 1)		1.70 (d, 0.5, 6.5)	0.89 (t, 2.4, 6.5)		253, 304	4.06, 3.54
XII	6.4–7.4 (m, 4)						0.92 (t, 3, 6.0)		258, 307	3.99, 3.46
XII-acetate	6.4–7.4 (m, 4)		5.20 (m, 1)				0.84 (t, 3, 6.0)	2.15 (s, 3)		
IX + XIII[k]	6.78 (s, 1), 5.71 (s, 1)	5.52 (q, 0.75, 6.5)		4.92 (m, 1)	3.77 (s, 3), 3.23 (s, 3)[k]	1.69 (d, 2.2, 6.5)	0.91 (t, 0.7, 6.0)		255, 275,[j] 321	3.90, 3.77, 3.85
IX + XIII[l]	6.62 (s, 1), 6.20 (s, 1)	5.55 (q, 1, 7)		5.40 (m, 1)	3.80 (s, 5.5)	1.75 (d, 2.5, 7)	0.93 (t)			
X	6.60 (s, 1), 6.08 (s, 1)	5.42 (q, 1, 7.0)			3.78 (s, 3), 3.73 (s, 3)	1.69 (d, 3, 7.0)			257.5, 321	3.97, 3.76
X-acetate	6.61 (s, 1), 6.09 (s, 1)	5.32 (q, 1, 7.0)	5.12 (m, 1)		3.82 (s, 3), 3.76 (s, 3)	1.47 (d, 3, 7.0)		1.93 (s, 3)	257.5, 320	3.97, 3.74
XIV	6.57 (s, 1), 6.09 (s, 1)				3.81 (s, 3), 3.75 (s, 3)		0.91 (t, 3, 5.5)		258, 321	3.96, 3.74

[a] Determined for solutions in $CDCl_3$ on a Varian A-60 spectrometer with Me_4Si (TMS) as internal reference standard. Chemical shifts are expressed in δ units measured downfield from the reference; s = singlet, d = doublet, t = triplet, q = quartet. Centers of gravity were estimated visually for all signals except the aromatic multiplets. Numbers in parentheses give estimates of the proton contents of the corresponding signals estimated by assuming the right aromatic proton content, followed, where appropriate, by coupling constants in cycles per second. Chemical shifts should be accurate to ±0.01 ppm, coupling constants to ±0.5 cps. [b] Determined for solutions in 95% ethanol recorded on a Perkin-Elmer 450 UV Visible NIR spectrophotometer. [c] When Δ^{21} is present. [d] When Δ^{21} is saturated. [e] Reference 24. [f] A. W. Sangster and K. L. Stuart, *Chem. Rev.*, **65**, 69 (1965), cite λ_{max} 254, 278, 288 mμ (log ε 4.10, 3.63, 4.54), the last value probably a misprint for 3.54. [g] Lit.[f] λ_{max} 265, 317 mμ (log ε 4.12, 3.55). [h] Reference 25. [i] Lit.[f] λ_{max} 267, 301 mμ (ε 4.08, 3.93). [j] Shoulder. [k] Data were determined for the benzene solvate (one-proton benzene singlet at δ 7.36). [l] Unsolvated product.

rearrangement,[5] of a Δ^{22}-23,24-secostrychnine intermediate, which, containing a terminal olefinic grouping, would be expected to undergo further reduction.[6] However, careful examination of the pmr spectra of a number of reduction products, obtained under a variety of conditions, failed to reveal the pattern of resonances expected for the $CH{=}CH_2$ grouping, and we consider that XI may equally be formed by direct metal–ammonia reduction of the Δ^{21} bond in VII. Examination of Dreiding models shows that it is sterically feasible for Δ^{21} reduction to be facilitated through cyclic donation of protons from the solvent through the C_{12}-hydroxyl group to anionic intermediates formed by electron addition to the double bond.[7] That reduction is less complete on the larger scale is attributable to the heterogeneous character of the reaction, because of the low solubility of strychnine in NH_3, and a consequent less efficient mixing of the substrate and the reducing agent.

The reduction of strychnidine, brucine, and brucidine under parallel conditions gave broadly similar results. Thus, strychnidine (II), with Na and methanol in liquid NH_3, gave XII; brucine (III), with Na and ethanol in liquid NH_3, gave a mixture of IX and XIII in a molecular ratio estimated as approximately 3:1; and brucidine, with Na and methanol in liquid NH_3, in one experiment gave X, and, in another involving a longer reaction time, the dihydro derivative XIV. The structures of these products were assigned chiefly on the basis of their pmr spectra (see Table I). Each reduction product or each constituent of a reduction product behaves as a single and presumably stereochemically homogeneous component on tlc (see Experimental Section). Interestingly, in the spectrum of the benzene-solvated mixture of IX and XIII (determined as usual in $CDCl_3$) the resonances of one aromatic proton, the C_{10}-proton, and one methoxyl group are shifted *ca.* 0.5 ppm upfield from their locations in the spectrum of the desolvated substance. The methoxyl shift at least is reminiscent of those observed for various aromatic methoxyl resonances when the solvent is changed from $CDCl_3$ to benzene.[8] If the effects arise from some type of complexing effect involving benzene (*cf.* ref 9) then the data bespeak a rather specific association, since approximately only 1 mole of benzene is present for every six alkaloid molecules, and the solvated mixture is dissolved in a large excess of $CDCl_3$. Notably, the IX–XIII mixture retains benzene even after recrystallization from acetone–ether. Chromatographic evidence indicates each constituent to be stereochemically homogeneous. The IX–XIII mixture was obtained free of solvent after distillation *in vacuo* but gave somewhat high values for carbon on elemental analysis (see Experimental Section). However, the mass spectrum (taken on the solvate) was characterized by ions of high relative abundance at *m/e* 380 and 382 corresponding to the loss of 1 mole of H_2O from each of the structures IX

(5) Reference 3, p 158, and references cited therein.

(6) Reference 3, p 212, and references cited therein.

(7) Reference 3, p 237.

(8) J. H. Bowie, D. W. Cameron, P. E. Schutz, D. H. Williams, and N. S. Bhacca, *Tetrahedron*, **22**, 1771 (1966); J. H. Bowie, J. Rouayne, and D. H. Williams, *J. Chem. Soc.*, 785 (1966).

(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 162, 170.

and XIII. Other ions at *m/e* 362 and 364 were consistent with the loss of 2 moles of H_2O from IX and XIII, respectively.

Biological Activities.—In view of the known analeptic and convulsant[10] properties of strychnine, it was of interest to establish whether any of the strychnine derivatives described here showed related effects. The 1:4 mixture of the hydroxysecostrychnidines VII and XI (containing *ca.* 80% of the latter), upon examination by the self-stimulation method[11] for its antidepressant effect upon the central nervous system of the rat, behaved very much like the clinically effective antidepressant imipramine[12,13] at a comparable dose, showing powerful amphetamine-potentiating (antidepressant) activity at a dose of 5 mg/kg, and well-marked tranquillizing activity at a dose of 25 mg/kg, both administered intraperitoneally. The tranquillizing effect was nicely reversed by amphetamine. Notably, there was no sign of a strychnine-like convulsant activity at either dose, and simple observation of the animals revealed no untoward side effects. This activity seems to be due to XI, since pure VII was inactive in the same test. That the C_{21}-ethyl group is necessary for antidepressant activity is indicated by the similar activity of the dihydrosecostrychnidine XII and its brucidine analog XIV, and the almost complete absence of activity of the Δ^{21} analog X. The first two compounds had approximately the same potency as the VII–XI mixture at the 5-mg/kg dose.

Experimental Section

Melting points were measured on a Kofler block and are corrected. Optical rotations were determined at 589 (sodium D line) and 436 mμ on *ca.* 1% solutions in $CHCl_3$ with the Zeiss Photoelectric precision polarimeter 0.005°. Thin layer chromatography (tlc) was conducted on silica gel chromatoplates prepared with rice-starch binder,[14] with irrigation by $CHCl_3$–C_6H_6 mixtures (3:2 by vol. unless stated otherwise) previously saturated with NH_4OH,[15] and processing of the chromatograms with the Dragendorff reagent.[16] Mass spectra were determined with an Atlas CH-4 mass spectrometer.

Strychnine and brucine, both homogeneous by tlc, were purchased from the Mallinckrodt Chemical Co., St. Louis, Mo., and Matheson, Coleman and Bell, East Rutherford, N. J., respectively. Strychnidine was prepared by reduction of strychnine with $LiAlH_4$[17] and had mp 248–251° [lit. 256° (*in vacuo*),[17,18] 246–248°,[18] 246°,[19] 258° (*in vacuo*)[20]], $[\alpha]^{23}D$ −79.7° ($CHCl_3$) [lit. $[\alpha]^{20}D$ −8.2° ($CHCl_3$),[8] $[\alpha]^{19}D$ −63° ($CHCl_3$)[20]]. 10-Dehydrobrucidine was prepared from brucine by reduction with $LiAlH_4$[21] and had mp 191–192° (lit.[21] 187.5–189°). We were unable to convert 10-dehydrobrucidine to brucidine with Raney nickel as previously described.[22]

Brucidine (IV).—Zinc dust (8 g) was added portionwise over 1 hr with vigorous stirring to dehydrobrucidine[22] (2 g) in 11 *N* HCl (50 ml). The solution was strongly basified with 10% aqueous NaOH (ice bath) and the product was extracted ($CHCl_3$) and recrystallized from methanol to give brucidine (1.5 g), mp 201–203° (lit. 203–203.5°,[23] 198–199°[18]), $[\alpha]^{23}D$ +66.2°, $[\alpha]^{23}_{436}$ +118°.

General Directions for the Reduction of Alkaloids.—Sodium was added piecemeal over 0.5–2.5 hr (time interval A) to a vigorously stirred suspension of the alkaloid in liquid ammonia containing methanol or ethanol. After a further 0–45 min (time interval B), NH_4Cl was added and the NH_3 was allowed to evaporate. Water was added to the residue, and, unless stated otherwise, the product was filtered off, dried, and recrystallized.

Reduction of Strychnine to VII and XI.—Materials used were strychnine (2 g), Na (1.5 g), NH_3 (300 ml), ethanol (2 ml), NH_4Cl (2 g). Time intervals were A, 45 min; B, 10 min. The product was recrystallized from ethyl acetate to give the mixture of 10ξ-hydroxy-23,24-secostrychnidine (VII) and 21ξ,22-dihydro-10ξ-hydroxy-23,24-secostrychnidine (XI) as needles (1.2 g); mp 164–166°; $[\alpha]^{23}D$ +21.4°, $[\alpha]^{23}_{436}$ +29°; tlc, two principal spots, R_f 0.38 and 0.22 with a trace of a third, R_f 0.09.

Anal. Calcd for $C_{21}H_{28}N_2O_2$, $C_{21}H_{26}N_2O_2$: C, 74.1, 74.5; H, 8.3, 7.7; N, 8.2, 8.3, respectively. Found: C, 74.1; H, 8.4; N, 8.2.

Reduction of Strychnine to VII.—Materials used were strychnine (20 g), Na (14 g), NH_3 (1.6 l.), ethanol (20 ml), NH_4Cl (5 g). Time intervals were A, 1.5 hr; B, 0 hr. The VII (9.0 g) had mp 158–162° (from ethyl acetate); $[\alpha]^{24}D$ +60.2°, $[\alpha]^{24}_{436}$ +126°; tlc, one major component R_f 0.38, with a trace of a second, R_f 0.45.

Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.5; H, 7.7. Found: C, 74.1; H, 7.7.

Reduction of Strychnidine to XII.—Materials used were strychnidine (25 g), Na (15 g), NH_3 (3 l.), methanol (24 ml), NH_4Cl (20 g). Time intervals were A, 2.5 hr; B, 15 min. The product was recrystallized from C_6H_6–EtOAc to give the XII (11.5 g) as a benzene solvate; mp 160–165° (softening above 120°). In similarly prepared samples, wider ranges of melting point, *e.g.*, 178–185° (softening above 165°), 175–200° (softening above 130°), were observed; tlc, one major component R_f 0.46, with a trace of a second, R_f 0.54.

Anal. Calcd for $C_{21}H_{28}N_2O \cdot 0.5C_6H_6$: C, 79.3; H, 8.6; N, 7.7. Found: C, 79.1; H, 8.4; N, 7.4.

An aliquot of the solvate was distilled at 230° (block) (2 mm) to give XII as a glass.

Anal. Calcd for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7. Found: C, 78.0; H, 8.7.

The **acetate** had mp 154–159° (from hexane); tlc ($CHCl_3$–C_6H_6, 7:3), one major spot R_f 0.58. An aliquot, after distillation at 195° (block) (2 mm) had mp 160° (softening above 130°) and showed ester but not amide carbonyl absorption in the infrared.

Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.4; H, 8.25; N, 7.6. Found: C, 75.2; H, 8.3; N, 7.9.

Reduction of Brucine to IX and XIII.—Materials used were brucine (5 g), Na (5 g), NH_3 (500 ml), ethanol (5 ml), NH_4Cl (10 g). Time intervals were A, 1 hr; B, 0 hr. The product, in benzene, was percolated through alumina and recrystallized from acetone–ether to give the mixture of 10ξ-hydroxy-23,24-secobrucidine (IX) and 21ξ,22-dihydro-10ξ-hydroxy-23,24-secobrucidine (XIII) as a solvate (1.5 g), mp 163–170°. An aliquot was distilled at 200–220° (block) (2 mm) to give the mixture as a glass; tlc, two major spots R_f 0.27 and 0.11 (trailing).

Anal. Calcd for $C_{23}H_{30}N_2O_4$, $C_{23}H_{32}N_2O_4$: C, 69.3, 69.0; N, 7.6, 8.0; M, 398, 400. Found: C, 70.0; H, 7.6; M − 18 (by mass spectrometry), 380, 382.

Reduction of Brucidine to X.—Materials used were brucidine (2 g), Na (3 g), NH_3 (300 ml), methanol (2 ml). Time intervals were A, 30 min; B, 10 min. The product was extracted with $CHCl_3$ and an aliquot was distilled at 190–210° (block) (2 mm) to give the 23,24-secobrucidine as a glass; tlc ($CHCl_3$–C_6H_6, 7:3), one component R_f 0.27.

Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.2; H, 7.9; N, 7.3. Found: C, 72.1; H, 8.3; N, 7.0.

The **acetate** formed a glass, bp 200° (block) (2 mm), one component R_f 0.43.

(10) A. Burger in "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 389.

(11) L. Stein, "Psychosomatic Medicine," J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, p 297; L. Stein and J. Seifter, *Science*, **134**, 286 (1961).

(12) W. Schindler and F. Haefliger, *Helv. Chim. Acta*, **37**, 472 (1954).

(13) R. Kuhn, *Schweiz. Med. Wochschr.*, **87**, 1135 (1957).

(14) L. L. Smith and T. Foell, *J. Chromatog.*, **9**, 339 (1962).

(15) L. Labler and V. Černý, *Collection Czech. Chem. Commun.*, **28**, 2932 (1963).

(16) H. Schriftman, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 111 (1959).

(17) P. Karrer, C. H. Eugster, and P. Waser, *Helv. Chim. Acta*, **32**, 2381 (1949).

(18) J. Tafel, *Ann.*, **301**, 285 (1898).

(19) G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1582 (1927).

(20) G. W. Kenner and M. A. Murray, *ibid.*, 406 (1950).

(21) S. P. Findlay, *J. Am. Chem. Soc.*, **73**, 3008 (1951).

(22) P. Karrer and H. Fleisch, *Helv. Chim. Acta*, **36**, 1529 (1953).

(23) J. M. Gulland, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1627 (1927).

Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.7; H, 7.6; M, 424. Found: C, 69.7; H, 7.6; M (by mass spectrometry), 424.

Reduction of Brucidine to XIV.—Materials used were brucidine (4 g), Na (3.5 g), NH_3 (400 ml), methanol (4 ml), NH_4Cl (4.0 g). Time intervals were A, 30 min; B, 45 min. The product was recrystallized from acetone to give the 21ξ,22-dihydro-23,24-secobrucidine as a solvate (2 g); mp 192–196°; one major spot R_f 0.11, with a trace of a second, R_f 0.16. The desolvated substance, prepared by drying *in vacuo*, had mp 195–202°.

Anal. Calcd for $C_{23}H_{32}N_2O_3$: C, 71.8; H, 8.4. Found: C, 71.6; H, 8.4.

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New Psychotropic Agents. VIII.[1] Analogs of Amitriptyline Containing the Normeperidine Group

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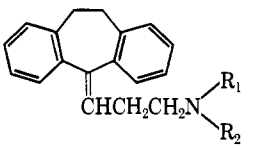
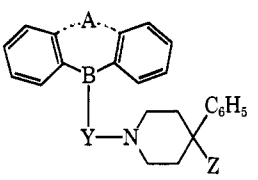
A series of compounds related to the previously reported 5-[3-(4-carbethoxy-4-phenylpiperidino)propylidene]-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene has been prepared. These include analogs in which the tricyclic ring and piperidino group were separated by one- to three-carbon side chains in differing states of oxidation. In several cases the corresponding reversed esters were also prepared. Related compounds were made in which the dibenzocycloheptene ring was replaced by an iminodibenzyl, a phenothiazinyl, or a benzhydryl grouping. The preparation of a number of novel intermediates is discussed including that of a dibenzocycloheptene 5-spiroepoxide. Analgetic testing showed that several of the compounds had activities in the range of morphine.

The preparation, in these laboratories, of a series of dibenzocycloheptenes possessing distinct psychotropic activities has been reported.[2] Two of the compounds, amitriptyline (Ia) and nortriptyline (Ib), have been used successfully in the treatment of depressive disorders.[3] One of the analogs which we had studied was Ic, in which the terminal amino function, NR_1R_2, formed part of the 4-carbethoxy-4-phenylpiperidine or normeperidine group. When the sparingly water-soluble hydrochloride salt of Ic was given intraperitoneally to mice and rats, it exhibited some of the pharmacological properties of the antidepressant drugs, but appeared to lack significant analgetic effects. The influence of the normeperidine group was seen, however, on subsequent oral administration. Due, possibly, to better absorption from the gastrointestinal tract (at large doses a portion of the unchanged compound had been found in the intraperitoneal cavity), it exhibited an analgetic action in the range between morphine and meperidine.

It is well known that replacement of the N-methyl moiety of meperidine by appropriate groups can lead to compounds with markedly enhanced analgetic activities.[4] On occasion it has been possible to dissociate the morphine-like effects of the parent drug to obtain agents which possess antiperistaltic[4] or antitussive[5] actions together with minimal or no narcotic properties. Accordingly, a series of compounds related to Ic was prepared having the common structural features shown in II. Those derived from the dibenzocycloheptene ring (A = CH_2CH_2 or CH=CH; B = carbon) carrying

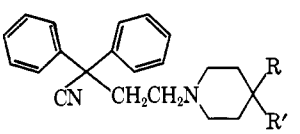




Ia, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$
c, NR_1R_2 = 4-carbethoxy-4-phenylpiperidino

II

a one- to three-carbon side chain, Y, in differing states of oxidation are listed in Table I. As well as the usual normeperidine group (Z = $CO_2C_2H_5$), we have also prepared some of the compounds in the form of their reversed esters (Z = $OCOC_2H_5$) in the hope of increasing the analgetic potency. Table II lists compounds where the dibenzocycloheptene ring has been replaced by a heterocycle, *viz.*, 5-iminodibenzyl or 10-phenothiazinyl. A series of related compounds derived from iminodibenzyl has been claimed to possess antipsychotic properties,[6] while 2-substituted 10-phenothiazinyl analogs of Ic exhibited antihypertensive activity.[7] Several compounds were prepared in which the bridging group, A, is absent; these benzhydryl analogs are listed in Table III. They are related to 2,2-diphenylbutyronitrile derivatives having antidiarrheal (IIIa)[8a] and



IIIa, R = C_6H_5; R′ = $CO_2C_2H_5$ (diphenoxylate)
b, R = piperidino; R′ = $CONH_2$ (pirinitramide)

(1) Part VII: M. A. Davis, G. Beaulieu, J. R. Watson, and M.-P. Charest, *J. Med. Chem.*, **9**, 860 (1966).

(2) (a) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. A. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962); (b) J. Stewart, M.-P. Charest, and F. Herr, *J. Med. Chem.*, **6**, 338 (1963).

(3) F. Häfliger and V. Burckhardt in "Psychopharmacological Agents," Vol. 4-I, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 35.

(4) R. A. Hardy, Jr., and M. G. Howell in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, N. Y., 1965, p 179.

(5) M. A. Davis, U. S. Patent, 3,094,528 (1963).

(6) Yoshitomi Pharmaceutical Industries, Ltd., British Patent 1,017,986 (1966); *Chem. Abstr.*, **64**, 17559 (1966).

(7) H. S. Lowrie, U. S. Patent 3,112,308 (1963).

(8) (a) P. A. J. Janssen, A. H. Jageneau, and J. Huygens, *J. Med. Pharm. Chem.*, **1**, 299 (1959); (b) C. van de Westeringh, P. Van Daele, B. Hermans, C. Van der Eycken, J. Boey, and P. A. J. Janssen, *ibid.*, **7**, 619 (1964).