seizure in drug-treated animals divided by the mean mg/kg of convulsant required to reach the same end point in controls) have been reported previously by Wolf and Stock.[17]

## References


(1) D. T. Witiak, S. K. Seth, E. R. Baizman, S. L. Weibel, and H. H. Wolf, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 31, 249 (1972).
(2) C. Hansch, *Accounts Chem. Res.*, 2, 232 (1969).
(3) P. Wiechert and G. Gollnitz, *Deut. Gesundheitsw.*, 25, 1126 (1970).
(4) D. T. Witiak, Z. Muhi-Eldeen, N. Mahishi, O. P. Sethi, and M. C. Gerald, *J. Med. Chem.*, 14, 24 (1971).
(5) P. S. Portoghese, *Annu. Rev. Pharmacol.*, 10, 51 (1970).
(6) E. Frommel, P. Gold-Aubert, and C. Fleury, *Arch. Int. Pharmacodyn.*, 122, 15 (1969).
(7) T. C. Butler, *J. Pharmacol. Exp. Ther.*, 104, 299 (1952).
(8) P. S. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafiee, *J. Med. Chem.*, 11, 12 (1968).
(9) J. Kovacs, H. N. Kovacs, and R. Ballina, *J. Amer. Chem. Soc.*, 85, 1839 (1963).
(10) H. Wolff and A. Berger, *ibid.*, 73, 3533 (1951).
(11) A. Buzas and C. Egnell, *Ann. Chim. (Paris)*, 10, 313 (1965).
(12) P. N. Yeoh and H. H. Wolf, *J. Pharm. Sci.*, 57, 340 (1968).
(13) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, 106, 319 (1952).
(14) L. A. Woodbury and V. D. Davenport, *Arch. Int. Pharmacodyn.*, 92, 97 (1952).
(15) H. H. Wolf, E. A. Swinyard, and L. S. Goodman, *J. Pharm. Sci.*, 51, 74 (1962).
(16) J. T. Litchfield, Jr., and L. Wilcoxon, *J. Pharmacol. Exp. Ther.*, 96, 99 (1949).
(17) H. H. Wolf and G. A. Stock, Jr., *J. Pharm. Sci.*, 55, 1455 (1966).


# Cycloalkane Spiroheterocyclic Compounds. 9. 8-(1,2,3,4-Tetrahydro-2-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]decanes and Related Compounds[1]


Jacques Maillard,* Michel Langlois, Pierre Delaunay, Tri Vo Van, Jacques Chenu,

*Department of Chemistry*

Robert Morin, Marguerite Benharkate, Chantal Manuel, and Françoise Motosso

*Department of Pharmacology, Laboratoires Jacques Logeais, 92-Issy-Les-Moulineaux, France.*

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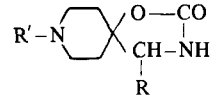
Several new 2-oxo-1-oxa-3,8-diazaspiro[4.5]decanes with 2-indanyl, 2-tetralyl, phenylcyclohexyl, and phenylcycloheptyl substitution on N-8 were prepared from the corresponding cyclanones. Other groups (2-indanylmethyl, 2-tetralylmethyl) were introduced in the same position by means of their halogenated derivatives. Some 8-(2-tetralyl) compounds were synthesized from 1-(2-tetralyl)-4-piperidone. The 2-tetralyl derivatives were found to be the most analgetic and adrenolytic. The relations between these activities and the structure of the substituent are discussed.


Among the 2-oxo-1-oxa-3,8-diazaspiro[4.5]decanes (**1**) described in a previous work,[1] the derivatives which contain an aralkyl group in position 8 were shown to be the most interesting. The best pharmacological activities (antiarrhythmic and analgetic) were obtained with $R' = C_6H_5CH_2CH_2$ (**1a**) or $C_6H_5(CH_2)_3$ (**1b**).



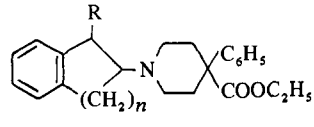
1a, $R' = C_6H_5CH_2CH_2$
1b, $R' = C_6H_5CH_2CH_2CH_2$

It appears that the aralkyl chain plays a definite role in ascribing to each of these two derivatives its own pharmacological profile. **1a** is mainly analgetic and central nervous system depressant, and **1b**, weakly analgetic, exerts good antiarrhythmic and hypotensive activities. The differences between their sites of action may be related to various orientations of the phenyl ring in relation to the piperidine or to the oxazolidine cycle which is perpendicular to the medium plane of piperidine.

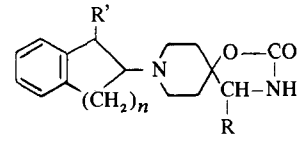
We wanted to assign a restricted conformation to this structure by replacing the aralkyl group by 2-indanyl (**3a**) or 2-tetralyl (**3b**) or a benzocycloheptyl ring (**3c** and **47**).

A similar hypothesis had previously led to derivatives of normeperidine **2**, as potential analgetics and antitussives.[2] 2-Indanylamine itself was found to be endowed with analgetic properties.[3]

Molecular models show that the plane of the aromatic

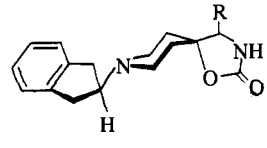


2, $n = 1$ or 2

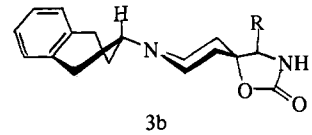


**3a**, $n = 1$
**3b**, $n = 2$
**3c**, $n = 3$

ring in **3b** is roughly parallel to the axis of the bond between the piperidine and the saturated cycle of tetralin, which takes the most likely half-chair conformation.[4] This gives to the molecule an elongated shape which cannot be taken by **3a**. Moreover, on account of the distance between the phenyl ring and the N atom, we could expect that **3b** would have pharmacological characteristics nearer those of **1a** than **1b**.



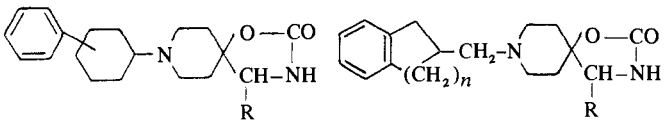
**3a**



**3b**

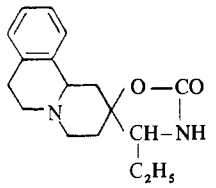
We then tried to obtain compounds more strictly related to **1b**, either by replacing the flexible chain $(CH_2)_n$ by cyclohexyl, substituted with $C_6H_5$ in various positions (type **4**), or by removing the indanyl or tetralyl groups from the N atom with a $CH_2$ link (type **5**).

In one example (compound **52**), the piperidine ring was involved in a benzo[*a*]quinolizine structure, which is known



4 5

to be related to interesting pharmacological properties.[5,6] The proof that compound **52** has the trans configuration can be obtained by examining the ir spectrum, which exhibits strong "Bohlmann bands" at 2760 and 2810 $cm^{-1}$.



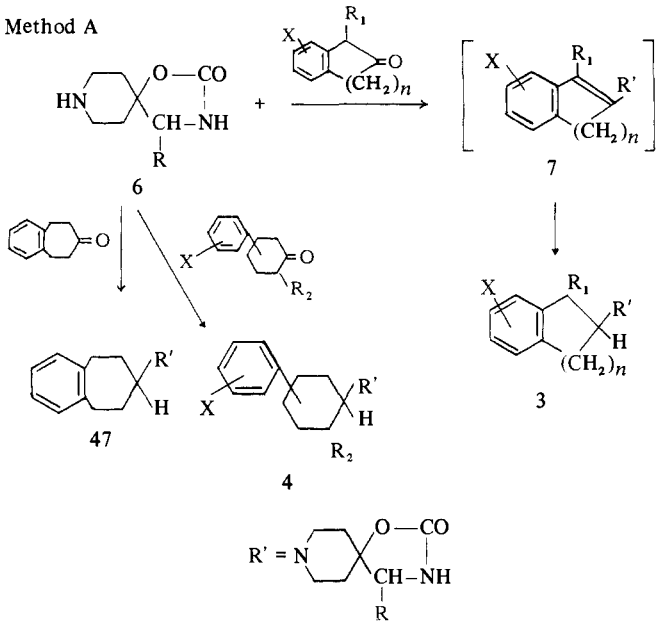
52

Chemistry. Most of the new compounds were obtained from 2-0x0-1-oxa-3,8-diazaspiro[4.5]decanes (**6**), the preparation of which was previously described.[1] The procedures for introduction of a substituent upon N-8 depend on the type of compounds.

Compounds **3**, **4**, and **47** were synthesized by reaction of a cyclanone with **6**, in the presence of acetic or *p*-toluenesulfonic acid, followed by catalytic hydrogenation or $NaBH_4$ reduction of an intermediate enamine (method A).

In one example, the enamine **7** (R = $C_2H_5$; R′ = X = H; *n* = 2) was isolated and purified. The catalytic hydrogenation proceeds slowly in normal conditions and was best achieved using acetic acid as solvent.

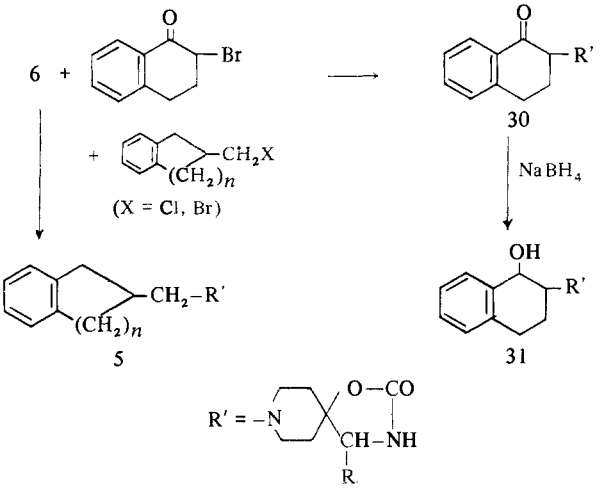
Method A



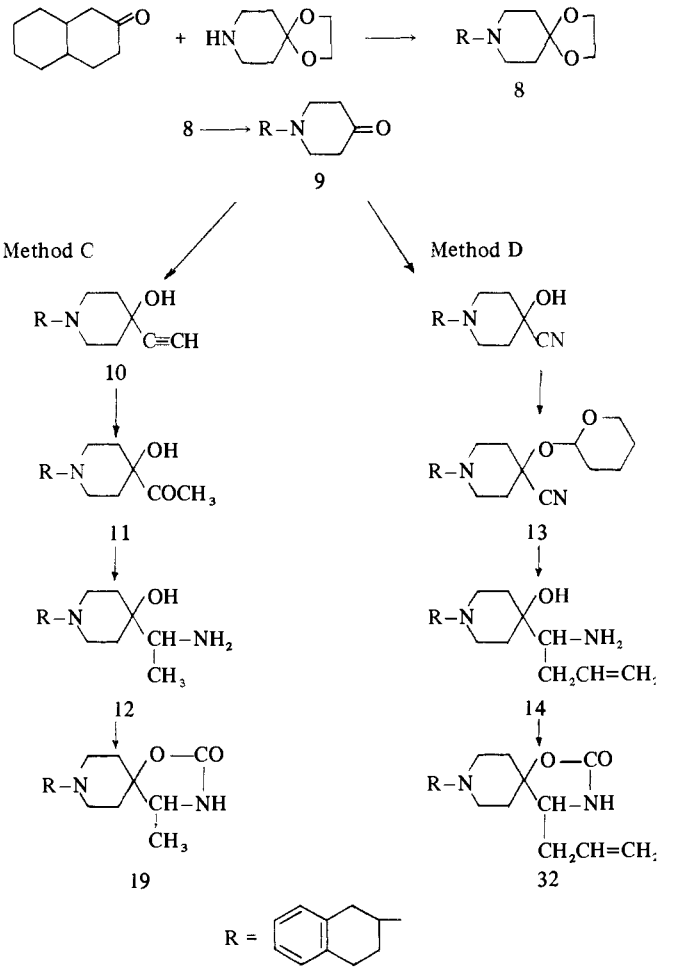
The cyclanones used as starting materials in this procedure were generally known products. The 2-tetralones substituted with X = alkoxy were prepared from corresponding 2-naphthols by the Birch reaction.[7] 6-Chloro-2-tetralone and 4,4-dimethyl-2-tetralone were obtained by cyclization of the corresponding phenacetyl chloride with ethylene or isobutene in the presence of $SnCl_4$.[8,9] 2-Tetralone was alcoylated in position 1 according to Stork.[10] 1-Propyl-2-indanone was synthetized by reaction of performic acid with 3-propylindene, following the method described for 2-indanone.[11] The ortho-$CH_3$- or -Cl-substituted 4-phenylcyclohexanones corresponding to **41** and **42** were prepared according to procedures used respectively for unsubstituted phenyl-4-cyclohexanones[12] or for its *p*-chloro derivative.[13]

Compound **30** (type **3**) and derivatives of type **5** were prepared by alkylation of **6** with a halide used in large excess (method B). The reduction of **30** with $NaBH_4$ leads to the hydroxylated derivatives **31**.

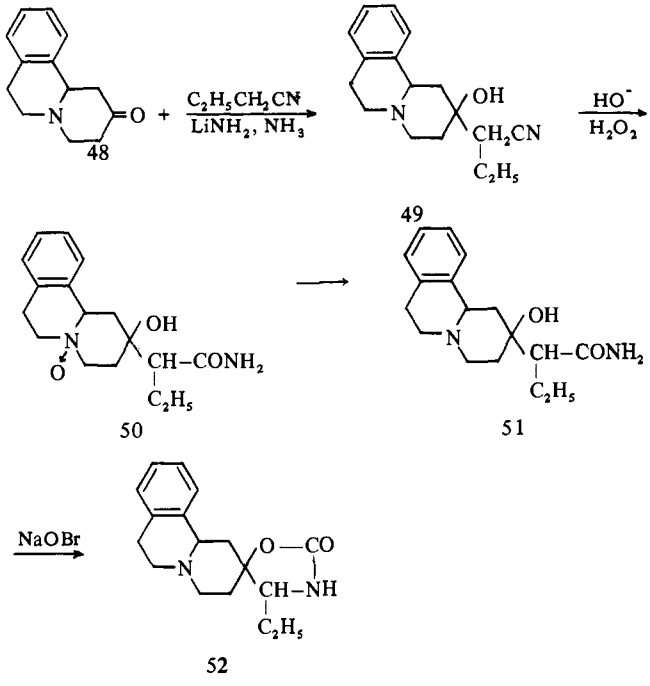
Method B



Some compounds of type **3** were synthetized from 1-(1,2,3,4-tetrahydro-2-naphthyl)-4-piperidone (**9**). It was the case for **19**, through the ethynyl intermediate **10** (method C), and for **32** where the allyl chain could not suffer the conditions of reductive alkylation and which was prepared according to the following method D, previously used for analogs.[14]



The benzo[*a*]quinolizine derivative **52** was obtained from the ketone **48** through reaction with butyronitrile and $LiNH_2$ in liquid $NH_3$, then transformation of hydroxynitrile **49** into amide and oxazolidinone, according to known procedures.[14]




48 49 50 51 52

Several compounds, such as **20** and other derivatives of type **3** in which R is not hydrogen, contain two asymmetric centers and hence two diastereoisomers. Those compounds were used as mixtures of the two diastereoisomeric forms.

**Biological Activity.** All the compounds were tested for their analgetic activity in mice, and their cardiovascular properties in dogs. Most of them produce a hypotension which can be ascribed to a strong antagonism toward adrenaline and noradrenaline, corroborated by *in vitro* tests.

It appears from Table I that among the compounds of type **3**, the most potent are the tetrahydronaphthyl derivatives, which are at the same time more analgetic and more adrenolytic than the indan (**15**, **16**) or benzocycloheptane (**36**) derivatives. In both pharmacological fields, the presence of substituents in either the cycloalkane or aromatic moieties reduces the activities, and sometimes lowers the hydrosolubility of salts, so that the compounds could not be administered by intravenous route (**22**, **25**, **26**, and **27**). Increasing activities are observed when R is changed from H or $CH_3$ to $C_2H_5$ (the same variation appears in compounds of type **4**, between **39** and **40**). However $C_6H_5$ is unfavorable in this position, as it was seen in the previous paper.[1]

The most interesting compound **20** is twice as analgetic as **1a** in the screening tests (writhing, hot plate). Moreover, **20** is a powerful and long-lasting adrenolytic, ranking above phentolamine, and has good antiarrhythmic properties, equal to **1a** and **1b**. It is to be noted that compounds **27** and **31**, which are potential metabolites of **20**, are inactive.

In the series of type **4** (Table II), **40** exerts about the same analgetic and adrenolytic activities as **20**, in spite of a greater distance between the N atom and the aromatic ring. It can be seen on the models that the preferential equatorial position of $C_6H_5$ enables it to be coplanar with the piperidine medium plane. Compounds **41** and **42**, in which such a position is hindered by ortho substitution, are definitely less active, especially in the analgetic test, while **43** is equivalent to **40**. The ortho and meta isomers **37** and **38** have much lower activities as was already found for the analgetic properties of phenylcyclohexylamines.[15]

Compounds of type **5** (Table III), **44–46**, although they have an *N*-phenethyl structure, are not very potent analgetics. They have significant adrenolytic activities, especially **46**. However, they lack the antiarrhythmic properties of **1b**, to which **46** is closely related.

## Discussion

The comparison of the analgetic activity of **20** ($ED_{50}$ 7.5 mg/kg) with those of **16** ($ED_{50}$ 35 mg/kg) and **44** or **46** ($ED_{50} > 30$ mg/kg) leads to the conclusion that the orientation of the phenyl ring with respect to the C–N bond is the main factor involved. As far as has been investigated, the distance between the N atom and the phenyl ring seems of lesser importance, since **40** has the same activity as **20**. Therefore, the differences previously reported[1] between **1a** ($ED_{50}$ 15 mg/kg) and **1b** ($ED_{50} > 30$ mg/kg) cannot be attributed only to the length of the aralkyl chain. The same conclusion can be made for the adrenolytic properties, which are probably responsible for the other pharmacological activities, such as the antiarrhythmic and analgetic, in spite of some evident discrepancies. Phentolamine is active in analgetic tests, as are several sympathomimetic amines. Tetrahydro-2-naphthylamine itself, which is a part of the most active compounds, was shown to interfere with noradrenaline release and to inhibit its reuptake.[16] Some of its derivatives were shown to be endowed with analgetic properties.[9]

The results of extensive studies on **20** suggest good hypotensive and vasodilating activities, and a better therapeutic index than with the standards used. This compound has been selected for clinical trials.

## Experimental Section

**4-Ethyl-8-(1,2,3,4-tetrahydro-2-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane (20) (Method A).** Compound 6 (R = $C_2H_5$) (45.5 g, 0.247 mole) and 37.8 g (0.259 mole) of 2-tetralone were dissolved in 800 ml of toluene and 0.5 ml of AcOH. The solution was heated under reflux, until the theoretical amount of $H_2O$ azeotropically carried off was recovered. After cooling, the ppt of enamine 7 (R = $C_2H_5$; X = R′ = H; $n$ = 2) was collected, washed with toluene and hexane, and dried: 73 g (95%); mp 254°. *Anal.* ($C_{19}H_{24}N_2O_2$) C, H, N.

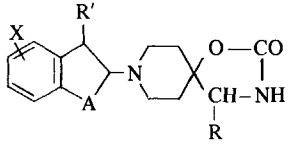
The intermediate enamine was dissolved in 300 ml of anhydrous $CH_3COOH$ and hydrogenated in the presence of 6 g of 5% Pd/C at 70° under atm pressure for 20 hr. The warm solution was filtered and evaporated. The residue was dissolved in 800 ml of $H_2O$ and 50 ml of concd HCl, washed with $C_6H_6$, decolorized with charcoal, and transformed into base which was crystd from *i*-PrOH: 58 g (78%).

**4-Ethyl-8-(1,2,3,4-tetrahydro-2-naphthylmethyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane (46) (Method B).** 2-Chloromethyl-1,2,3,4-tetrahydronaphthalene (28 g, 0.155 mole) and 9 g (0.049 mole) of compound 6 (R = $C_2H_5$) were heated at 120–130° for 17 hr. After cooling, the mixt was triturated with HCl ethereal soln, and the hydrochloride ppt was collected, decolorized with charcoal in hot aqueous soln, and transformed into base. The base was crystd from MeCN: 4.15 g (26%).

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-ethylenedioxypiperidine (8).** 4-Ethylenedioxypiperidine[17] (50 g, 0.35 mole) and 55.1 g (0.377 mole) of 2-tetralone were dissolved in toluene (500 ml) and AcOH (0.5 ml), and heated under reflux for 18 hr. After evaporation of the solvent, the residue was dissolved in EtOH (500 ml) and hydrogenated with 5% Pd/C, at 20° under atm pressure. The filtered soln was evaporated and the oil was distd: bp 175–180° (0.5 mm). *Anal.* ($C_{17}H_{23}NO_2$) C, H, N.

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-piperidone (9).** A soln of 82 g (0.3 mole) of 8 in 2 *N* HCl (850 ml) was heated under reflux for 5 hr. After washing with $C_6H_6$, the soln was made alk, and the oil was extd with ether. The ketone was purified through its bi-

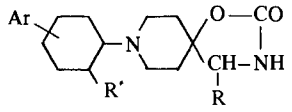
Table I




| No. | A | R | R' | X | Method | Yield, % | Crystn solvent | Mp, °C | Formula[a] | Analgetic act. in mice, $ED_{50}$, mg/kg po[b] | α-Adrenolytic act. in dogs: Doses provoking[c] Adrenaline inhib | Adrenaline reversal |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 15 | $CH_2$ | H | $n$-$C_3H_7$ | H | A | 40 | $H_2O$–MeOH | 168 | $C_{19}H_{26}N_2O_2$[i] | 75 | Inactive | |
| 16 | $CH_2$ | $C_2H_5$ | H | H | A | 70 | MeOH | 254 | $C_{18}H_{24}N_2O_3$ | 35 | 5 iv (50%) | |
| 17 | $(CH_2)_2$ | H | H | H | A | 44 | $i$-PrOH | 211 | $C_{17}H_{22}N_2O_2$ | 22 | 0.5 iv (50%) | |
| 18 | $(CH_2)_2$ | H | H | 7-$OCH_3$ | A | 26 | $i$-PrOH, then MeCN | 173–175 | $C_{18}H_{24}N_2O_3$ | 41 | | 5 iv |
| 19 | $(CH_2)_2$ | $CH_3$ | H | H | C | 38[d] | $i$-PrOH | 185–187 | $C_{18}H_{24}N_2O_2$ | 25 | 0.5 iv (100%) | 1 iv |
| 20 | $(CH_2)_2$ | $C_2H_5$ | H | H | A | 75 | $i$-PrOH | 200 | $C_{19}H_{26}N_2O_2$ | 7.5 | 0.1 iv (50–90%) | 0.25 iv |
| | | | | | | | | | | | | 5 id |
| 21 | $(CH_2)_2$ | $C_2H_5$ | H | H[e] | | | | 188[f] | $C_{21}H_{31}ClN_2O_2$ | Inactive | | |
| 22 | $(CH_2)_2$ | $C_2H_5$ | H | 6-Cl | A | 24 | | 176 | $C_{19}H_{25}ClN_2O_2$[j] | 30 | 10 id (50%) | |
| 23 | $(CH_2)_2$ | $C_2H_5$ | H | 5-$OCH_3$ | A | 24 | Dioxane | 238 | $C_{20}H_{28}N_2O_3$ | 80 | 0.1 iv (80%) | 0.5 iv |
| 24 | $(CH_2)_2$ | $C_2H_5$ | H | 6-$OCH_3$ | A | 45 | EtOH | 180–182 | $C_{20}H_{28}N_2O_3$ | 30 | | |
| 25 | $(CH_2)_2$ | $C_2H_5$ | H | 7-$OCH_3$ | A | 27 | THF, then MeCN | 194 | $C_{20}H_{28}N_2O_3$ | 25 | | 2 id |
| 26 | $(CH_2)_2$ | $C_2H_5$ | H | 7-$OC_2H_5$ | A | 49 | | 165–166 | $C_{21}H_{30}N_2O_3$ | >30 | 10 id (100%) | |
| 27 | $(CH_2)_2$ | $C_2H_5$ | H | 7-OH | | 57 | | 210 | $C_{19}H_{26}N_2O_3$ | 270 | 50 id (50%) | |
| 28 | $(CH_2)_2$ | $C_2H_5$ | $CH_3$ | H | A | 45 | EtCOMe | 185 | $C_{20}H_{28}N_2O_2$ | >100 | | |
| 29 | $(CH_2)_2$ | $C_2H_5$ | $n$-$C_3H_7$ | H | A | 34 | EtOAc | 167 | $C_{22}H_{32}N_2O_2$ | >100 | | 2 iv |
| 30 | $(CH_2)_2$ | $C_2H_5$ | =O | H | B | 40 | MeCN | 232[f] | $C_{19}H_{24}N_2O_3$ | >100 | Inactive | |
| 31 | $(CH_2)_2$ | $C_2H_5$ | OH | H | | 70 | MeCN | 220 | $C_{19}H_{26}N_2O_3$ | >100 | Inactive | |
| 32 | $(CH_2)_2$ | $CH_2CH{=}CH_2$ | H | H | D | 29[g] | | 149 | $C_{20}H_{26}N_2O_2$ | | 0.1 iv (50%) | |
| 33 | $(CH_2)_2$ | $C_6H_5$ | H | H | A | 21 | $i$-PrOH | 212 | $C_{23}H_{26}N_2O_2$ | 70 | 1 iv (50%) | |
| 34 | $(CH_2)_2$ | $C_6H_5$ | H | 7-$OCH_3$ | A | 36 | MeCN | 188–192 | $C_{24}H_{28}N_2O_3$ | 130 | 5 iv (70%) | |
| 35 | $C(CH_3)_2CH_2$ | $C_2H_5$ | H | H | A | 30 | MeCN | 196–197 | $C_{21}H_{30}N_2O_2$ | | | 5 iv |
| 36 | $(CH_2)_3$ | $C_2H_5$ | H | H[h] | A | 73 | MeCN then $i$-PrOH | 201–203 | $C_{20}H_{28}N_2O_2 \cdot HCl$ | >30 | 0.1 iv (50%) | 0.5 iv |
| | Codeine phosphate | | | | | | | | | 70 | | |
| | Phentolamine | | | | | | | | | 15 | 0.5 iv (50%) | 1 iv |

[a] Analytical results were within ±0.4% of theoretical values. [b] Koster–Anderson.[18] [c] Compound administered by intravenous (iv) or intraduodenal (id) route 10 min before iv injection of 2.5 μg/kg of adrenaline. [d] Calculated from compound 9. [e] Chloroethylate. [f] With decomposition. [g] Calculated from compound 13. [h] Hydrochloride. [i] H: calcd, 8.04; found, 8.5. [j] Cl: calcd, 10.16; found, 10.6.

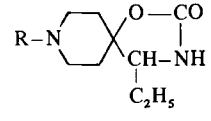
**Table II**

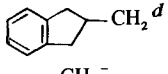
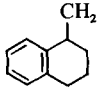
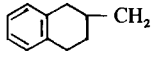
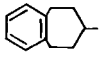


| No. | Ar | R | R′ | Method | Yield, % | Crystn solvent | Mp, °C | Formula[a] | Analgetic act. in mice, $ED_{50}$ mg/kg po[b] | α-Adrenolytic act. in dogs: Doses provoking[c] Adrenaline inhib | α-Adrenolytic act. in dogs: Doses provoking[c] Adrenaline reversal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 37 | 2-$C_6H_5$ | $C_2H_5$ | H | A | 28 | $C_6H_6$ | 142–145 | $C_{21}H_{30}N_2O_2$ | >100 | Inactive | |
| 38 | 3-$C_6H_5$ | $C_2H_5$ | H[d] | A | 32 | | 238[e] | $C_{21}H_{30}N_2O_2$·HCl | >30 | 2 iv (100%) | |
| 39 | 4-$C_6H_5$ | H | H | A | 70 | EtCOMe | 176–180[e] | $C_{19}H_{27}N_2O_2$ | >30 | 1 iv (50%) | |
| 40 | 4-$C_6H_5$ | $C_2H_5$ | H[d] | A | 45 | $H_2O$ | 280[e] | $C_{21}H_{30}N_2O_2$·HCl[f] | 8 | 0.1 iv (75%) | 0.25 iv |
| 41 | 4-  | $C_2H_5$ | H[d] | A | 37 | EtOH | 280[e] | $C_{22}H_{32}N_2O_2$·HCl | 20 | 0.5 iv (90%) | |
| 42 | 4-  | $C_2H_5$ | H[d] | A | 38 | Dil HCl | 305[e] | $C_{21}H_{29}ClN_2O_2$·HCl | 20 | 0.1 iv (90%) | 0.5 iv |
| 43 | 4-$C_6H_5$ | $C_2H_5$ | $CH_3$ | A | 43 | MeCN | 180 | $C_{22}H_{32}N_2O_2$ | <10 | 0.5 iv (50%) | |

[a–c]See footnotes in Table I. [d]Hydrochloride. [e]With decomposition. [f]C: calcd, 66.56; found, 66.0.

**Table III**



| No. | R | Method | Yield, % | Crystn solvent | Mp, °C | Formula[a] | Analgetic act. in mice, $ED_{50}$ mg/kg po[b] | α-Adrenolytic act. in dogs: Doses provoking[c] Adrenaline inhib | α-Adrenolytic act. in dogs: Doses provoking[c] Adrenaline reversal |
|---|---|---|---|---|---|---|---|---|---|
| 44 |  | B | 39 | 1 *N* HCl | 252[e] | $C_{19}H_{26}N_2O_2$·HCl | >30 | 0.5 iv (25%) | 1 iv |
| 45 |  | B | 8 | MeCN | 146–148 | $C_{20}H_{28}N_2O_2$ | 90 | 0.5 iv (90%) | 1 iv |
| 46 |  | B | 26 | MeCN | 160–162 | $C_{20}H_{28}N_2O_2$ | 40 | | 0.5 iv |
| 47 |  | A | 38 | MeCN, then *i*-PrOH | 191 | $C_{20}H_{28}N_2O_2$ | Inactive | Inactive | |

[a–c]See footnotes in Table I. [d]Hydrochloride. [e]With decomposition.

sulfite addn compd by shaking the ethereal soln with $NaHSO_3$ (aqueous soln $d = 1.28$). The ppt was collected, washed with EtOH and $Et_2O$, and decompd by shaking with 50 g of NaOH in 600 ml of $H_2O$ and 300 ml of $Et_2O$. The evapn of $Et_2O$ leaves 55.7 g of light yellow cryst product: mp 78° (80%). *Anal.* ($C_{15}H_{19}NO$) C, H, N. This compd was stored as its bisulfite addn compd.

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-hydroxy-4-ethynylpiperidine (10) (Method C).** 9 (37.5 g, 0.164 mole) dissolved in $Et_2O$ (300 ml) was added to a soln of 2.4 g of Na in liquid $NH_3$ (500 ml) satd with anhyd acetylene. The mixt was agitated 2 hr, then hydrolyzed with 125 ml of $H_2O$ and 40 ml of concd HCl. The aqueous phase was sepd, made alk, and extd with $CHCl_3$. The residue after evapn was crystd from toluene: 31.7 g (76%); mp 132–134°. *Anal.* ($C_{17}H_{21}NO$) C, H, N.

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-hydroxy-4-acetylpiperidine (11).** A mixt of 31.7 g (0.124 mole) of 10, 37.4 g of concd $H_2SO_4$, and 1.25 g of HgO in MeOH (27 ml) and $H_2O$ (35 ml) was heated under reflux for 4 hr, adding 1 g of HgO every hour. The soln was dild with $H_2O$ (300 ml), decolorized with C, and made alk. The ppt was collected and extd with boiling $Et_2O$. The evapn of $Et_2O$ leaves 26.6 g (78%) of crystd product: mp 124–125°. *Anal.* ($C_{17}H_{23}NO_2$) C, H, N.

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-hydroxy-4-(1-aminoethyl)-piperidine (12).** 11 (26 g, 0.095 mole) was dissolved in 200 ml of EtOH satd with $NH_3$ at −10° and hydrogenated with 5 g of Raney nickel at 100° under 1700 psi for 7 hr. The crude oil (26 g, 100%) after evapn of EtOH was used without further purification.

**4-Methyl-8-(1,2,3,4-tetrahydro-2-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane (19).** A soln of 20 g (0.073 mole) of the crude amine 12 in toluene (150 ml) was shaken with 28 g of KOH dissolved in $H_2O$ (225 ml) and treated with 115 ml of a 20% toluene soln of $COCl_2$, slowly added with cooling at 10–15°. After agitation for 3 hr, the mixt was made strongly alkaline, and the ppt was collected and crystd from *i*-PrOH: 13.9 g (63.5%).

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-tetrahydropyranyloxy-4-cyanopiperidine (13) (Method D).** The 9 bisulfite addn compd (25 g, 0.075 mole), dissolved in $H_2O$ (65 ml), was treated with 18.3 g of NaCN in 60 ml of $H_2O$ and strongly agitated for 2 hr. The ppt was collected, washed, and dried under vacuum. The crude unstable cyanhydrin, identified by its ir spectrum, was transformed into the hydrochloride in anhydr $Et_2O$ (quant yield).

This hydrochloride (23 g, 0.075 mole) was heated with 165 ml of tetrahydropyran, 45 ml of DMSO, and 5 ml of anhyd HCl ethereal soln, for 20 hr at 60–65°. After cooling, the ppt was collected and transformed into base which was crystd from *i*-PrOH: 7.2 g (28%); mp 95°. *Anal.* ($C_{21}H_{28}N_2O_2$) C, H, N.

**1-(1,2,3,4-Tetrahydro-2-naphthyl)-4-hydroxy-4-(1-amino-3-butenyl)piperidine (14).** 13 (16.8 g, 0.05 mole), dissolved in THF (100 ml), was added, at 0°, to allylmagnesium bromide prepared from 14.5 g of Mg and 12 g (0.1 mole) of allyl bromide in 50 ml of $Et_2O$. After 15 hr, the mixt was hydrolyzed with 7.4 g of $NH_4Cl$ in 50 ml of $H_2O$. The ethereal phase was evapd, and the residual oil was dissolved in MeOH (80 ml) and treated with 7.6 g (0.2 mole) of $NaBH_4$, added by small fractions, at 5°. After 1 hr at 5° and 2 hr under reflux, the soln was made alk with 20 g of NaOH in 50 ml of $H_2O$ and extd with $Et_2O$. The amine is separated as hydrochloride, by addn of anhyd HCl ethereal soln, and is transformed into an oily base: yield 13.7 g (91%) of crude product.

**4-Allyl-9-(1,2,3,4-tetrahydro-2-naphthyl)-2-oxo-1-oxa-3,8-diazaspiro[4.5]decane (32).** Crude amine 14 (13.7 g), dissolved in toluene (150 ml), was treated with $COCl_2$ and KOH aqueous soln as described for compound 19. The aqueous phase was decanted and extd with ether. The organic layers were joined together and evaporated, and the oily residue (14 g) crystd spontaneously in the cold. After trituration with $Et_2O$, 4.7 g of pure compd was obtained (32%): mp 149°.

**2-Hydroxy-2-(1-cyanoethyl)-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (49).** Into a soln of $LiNH_2$ (from 3.45 g of Li) in liquid $NH_3$ (460 ml) were introduced successively 34.5 g (0.5 mole) of butyronitrile, within 2 min, and then 20 g (0.1 mole) of ketone 48,[5] dissolved in $Et_2O$ (150 ml), within 2 min. The mixt was agitated 1 hr, added to 32 g (0.6 mole) of $NH_4Cl$, and evaporated. The residue was taken up with $H_2O$ and extd with $Et_2O$. The ethereal soln was extd with 2 *N* HCl, from which the base was released, obtained as an oil, and distd: bp 180–182° (0.2 mm). The distd product was crystd in *i*-$Pr_2O$: 13.5 g (50%); mp 146–160°. *Anal.* ($C_{17}H_{22}N_2O$) C, H, N.

**2-Hydroxy-2-(1-carbamylpropyl)-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine-5-Oxide (50).** 49 (40 g, 0.148 mole) was dissolved in MeOH (150 ml) with 2 *N* NaOH (74 ml) and 30% $H_2O_2$ (74 ml). After 20 hr at 20°, MeOH was evaporated, dild with 100 ml of $H_2O$, and passed on resin Dowex 50. After elution with 1 *N* $NH_4OH$ and evapn of the soln, the residue was triturated with MeCN and crystd in *tert*-BuOH: 20 g (46%); mp 270°. *Anal.* ($C_{17}H_{24}N_2O_3$) C, H, N.

**2-Hydroxy-2-(1-carbamylpropyl)-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (51).** *N*-Oxide 50 (17.5 g, 0.06 mole) was hydrogenated in EtOH (200 ml) with 5 g of 5% Pd/C at 50° under atm pressure (10 hr). The residue after evapn of EtOH was taken up with $Et_2O$. An unsoluble compd was filtered off, and the product was obtained by evapn of $Et_2O$ as an amorphous product and used without further purification: 15.5 g (89%).

**4-Ethyl-5-spiro(1,2,3,4,6,7-hexahydro)-11b*H*-benzo[*a*]quinolizin-2-yloxazolidin-2-one (52).** Crude 51 (15.5 g, 0.054 mole) was dissolved, at 0°, in a fresh soln of NaOBr (from 11.5 g, 0.072 mole, of bromine and 300 ml of NaOH). The soln was agitated 1 hr at 5°, then 2 hr at 50°. After cooling, 10 g of ppt was collected and crystd from a mixture of $C_6H_6$-*i*-$Pr_2O$ (20:40), then from $H_2O$–MeOH (1:1): 4.5 g (29%); mp 128–132°: *Anal.* ($C_{17}H_{22}N_2O_2$) C, H, N.

## References


(1) J. Maillard, M. Langlois, P. Delaunay, T. Vo Van, G. Garcia, R. Morin, P. Eskenazi, M. Benkarkate, C. Manual, and F. Motosso, *Chim. Ther.*, in press (paper 8).
(2) J. R. Geigy, French Patent 2645 M (June 28, 1963); Swiss Patent 408,005 (March 30, 1962).
(3) L. B. Witkin, L. F. Heubner, F. Galdi, E. O. Keefe, P. Spitaletta, and A. J. Plummer, *J. Pharmacol. Exp. Ther.*, 133, 400 (1961).
(4) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1966, p 109.
(5) A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, 51, 119 (1958).
(6) A. Brossi, L. H. Chopard-Dit-Jean, and O. Schnider, *ibid.*, 51, 1793 (1958).
(7) N. A. Nelson, R. S. P. Hsi, J. M. Schuck, and L. D. Kahn, *J. Amer. Chem. Soc.*, 82, 2573 (1960).
(8) A. Rosowsky, J. Battaglia, K. K. N. Chen, and E. J. Modest, *J. Org. Chem.*, 33, 4288 (1968).
(9) A. R. Martin, A. P. Parulkar, D. J. Gusseck, L. J. Anderson, G. L. Grunenwald, and A. I. White, *J. Pharm. Sci.*, 58, 340 (1969).
(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrel, *J. Amer. Chem. Soc.*, 85, 207 (1963).
(11) W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, 29, 1723 (1964).
(12) E. C. Horning, M. G. Horning, M. S. Fish, and M. W. Rutenberg, *J. Amer. Chem. Soc.*, 74, 773 (1952).
(13) N. L. Allinger and S. Greenberg, *ibid.*, 81, 5733 (1959).
(14) J. Maillard, P. Delaunay, M. Langlois, and T. Vo Van, *Bull. Soc. Chim. Fr.*, 1389 (1970).
(15) G. Cantarelli, *et al.*, *Farmaco, Ed. Sci.*, 24, 123 (1969).
(16) J. Bruinvels, *Brit. J. Pharmacol.*, 42, 281 (1971).
(17) J. M. McManus, J. W. McFarland, C. F. Gerber, W. M. McLamore, and G. D. Laubach, *J. Med. Chem.*, 8, 766 (1965).
(18) E. Koster and M. Anderson, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, 18, 412 (1959).