References

(1) P. W. Feit, O. B. T. Nielsen, and N. Rastrup-Andersen, *J. Med. Chem.*, **16**, 127 (1973) (paper 4).
(2) P. W. Feit, *ibid.*, 14, 432 (1971).
(3) P. W. Feit and O. B. T. Nielsen, *ibid.*, **15**, 83 (1972).
(4) J. B. Wright, *J. Heterocycl. Chem.*, **5**, 453 (1968).
(5) P. W. Feit, H. Bruun, and C. K. Nielsen, *J. Med. Chem.*, **13**, 1071 (1970).
(6) P. W. Feit, O. B. T. Nielsen, and H. Bruun, *ibid.*, **15**, 437 (1972).
(7) E. H. Østergaard, M. P. Magnussen, C. K. Nielsen, E. Eilertsen, and H.-H. Frey, *Arzneim.-Forsch.*, **22**, 66 (1972).
(8) P. W. Feit, K. Roholt, and H. Sørensen, *J. Pharm. Sci.*, **62**, 375 (1973).
(9) J. Krieglstein and G. Kuschinsky, *Arzneim.-Forsch.*, **18**, 287 (1968).

Analgetics Based on the Pyrrolidine Ring. 8

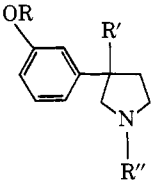
Ralph E. Bowman, Harry O. J. Collier, Peter J. Hattersley, Ian M. Lockhart,*† David J. Peters, Cyril Schneider, Nigel E. Webb, and Michael Wright

Chemical and Pharmacological Research Departments, Research and Development Division, Parke, Davis and Company, Hounslow, Middlesex, England.

Received November 9, 1972

A group of *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols and related compounds has been synthesized for evaluation as potential nonaddicting analgesic drugs. The compounds have been tested in mice and many show an antinociceptive effect in an abdominal constriction (writhing) test and, in addition, antagonize morphine in the tail pressure test. The biological results are discussed in relation to chemical structure.

The present paper describes some chemical and pharmacological properties of a series of 1-(cycloalkylalkyl)pyrrolidines [particularly 1-(cyclopropylmethyl)pyrrolidines of type (I)] (where, for example, R″ = CH_2-c-C_3H_5). Many of these compounds proved to be antinociceptive agents in abdominal constriction (writhing) tests and simultaneously have the ability to antagonize the effects of morphine in the tail pressure test. Pertinent structure–activity relationships are discussed. A detailed report on the pharmacological and chemical properties of *levo*-*m*-[1-(cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol monosuccinate (I, R = H; R′ = CH_2CHMe_2; R″ = CH_2-c-C_3H_5), also referred to as CI 747 succinate, is being published elsewhere.[1]



I

Chemistry and Experimental Section

The synthetic procedures used are summarized below. More detailed descriptions for some particular examples have been previously given.[2] The preparation of 3-alkyl-3-*m*-methoxyphenylpyrrolidines has been previously described.[3,4]

***m*-[3-Alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols. Method A.** N-Acylation of a 3-alkyl-3-(*m*-methoxyphenyl)pyrrolidine [or a 3-alkyl-3-(*m*-isopropoxyphenyl)pyrrolidine] with cyclopropanecarboxylic acid chloride (or with cyclopropanecarboxylic acid using the mixed anhydride method) was followed by reduction of the amide with $LiAlH_4$. Subsequent conversion of the 3-alkyl-1-(cyclopropylmethyl)-3-(*m*-methoxyphenyl)pyrrolidine [or the 3-alkyl-1-(cyclopropylmethyl)-3-(*m*-isopropoxyphenyl)pyrrolidine] to the *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]-phenol was effected by the use of boron tribromide[5] or, in the case of the (*m*-isopropoxyphenyl)pyrrolidine (compounds 18 and 19), with refluxing 6 *N* HCl.

Method B. N-Acylation of a 3-alkyl-3-(*m*-methoxyphenyl)pyrrolidine was followed by O-demethylation using boron tribromide. The phenolic amide was reduced to the corresponding *m*-[3-alkyl-1-(cycloalkylalkyl)3-pyrrolidinyl]phenol using $LiAlH_4$.

Method C. O-Demethylation of a 3-alkyl-3-*m*-(methoxyphenyl)-pyrrolidine with boron tribromide at −60°, or with refluxing HBr, afforded the corresponding *m*-(3-alkyl-3-pyrrolidinyl)phenol which, on N-acylation followed by reduction with $LiAlH_4$, gave the required *m*-[3-alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenol.

Method D. 3-Alkyl-3-(*m*-methoxyphenyl)pyrrolidines were N-alkylated by a method similar to that previously described.[6] O-Demethylation was effected with boron tribromide.

Optical Resolution of *m*-[1-(Cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol. Method E. *m*-[1-(Cyclopropylmethyl)-3-isobutyl-3-pyrrolidinyl]phenol was resolved by fractional crystallization of its salt with (−)-di-*p*-toluoyl-D-tartaric acid from EtOH. The salt of the (−) enantiomer crystallized first. Liberation of the base enriched in the (+) enantiomer from the salt in the mother liquors, followed by fractional crystallization of its salt with (+)-di-*p*-toluoyl-L-tartaric acid, led to the isolation of the (+) enantiomer.

O Esters. Method F. *m*-[3-Alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols were converted to the O esters by the action of an acid anhydride in pyridine.

Method G. As an alternative route to the O esters, the *m*-(3-pyrrolidinyl]phenols were converted to the O esters by the action with the acid chloride in the presence of triethylamine.

***m*-(1-Cyclopropyl-3-propyl-3-pyrrolidinyl)phenol. Method H.** 2-(*m*-Methoxyphenyl)-2-propylsuccinic acid (prepared from the corresponding imide by alkaline hydrolysis) was converted to the anhydride by a method similar to that described by Horning and Finelli.[7] Refluxing the anhydride with cyclopropylamine for 30 min afforded *N*-cyclopropyl-2-(*m*-methoxyphenyl)-2-propylsuccinimide which was O-demethylated with boron tribromide and the succinimide converted to the pyrrolidine by reduction with $LiAlH_4$ in Et_2O.

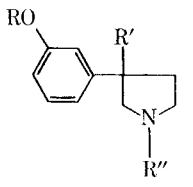
3-[*m*-(Allyloxy)phenyl]-1-(cyclopropylmethyl)-3-propylpyrrolidine. Method I. *m*-[1-(Cyclopropylmethyl)-3-propyl-3-pyrrolidinyl]phenol was converted to the O-allyl derivative by the action of allyl bromide in the presence of NaH.

The physicochemical properties of the compounds prepared for biological evaluation are listed in Table I.

Pharmacological Methods. Antinociceptive activity was measured using the mouse abdominal constriction test as described by Collier, *et al.*,[8] in which acetylcholine (3.2 mg/kg) was the intraperitoneal challenge substance. Antimorphine activity was measured in a mouse tail pressure test based on the method of Bianchi and Franceschini,[9] using a special apparatus described by Collier.[10] The test drug was administered subcutaneously in solution together with a dose of morphine (22.2 mg/kg) having an antinociceptive effect in 95% of animals treated. A median effec-

† Address correspondence to this author at Prochem, The British Oxygen Company, Ltd., London, SW19 3UF, England.

Table I. *m*-[3-Alkyl-1-(cyclopropylmethyl)-3-pyrrolidinyl]phenols and Related Compounds



No.	R	R′	R″	Method	Mp or bp (mm),[a] °C	Nature	Yield, %	Formula[b]	Antinociceptive activity, ED_{50}, mg/kg sc[y]	Morphine antagonism, ED_{50}, mg/kg sc[z]
1	Me	Pr	CH_2-c-C_3H_5	A	132–136 (0.5)	*h*	86	$C_{18}H_{27}NO$	10 (7.8–13)	>20
2	H	Me	CH_2-c-C_3H_5	B	69–70	*j*, *m*	68	$C_{18}H_{21}NO$	20 (12–34)	0.90 (0.53–1.7)
3	H	Et	CH_2-c-C_3H_5	B	98–100	*k*, *n*	70	$C_{16}H_{23}NO$	0.58 (0.27–0.98)	1.4 (0.88–2.1)
4	H	Pr	CH_2-c-C_3H_5	A, B	164–166 (0.35)[c]	*i*	70, 89	$C_{17}H_{25}NO$	0.24 (0.2–0.3)	3.2 (1.9–5.8)
5	H	Pr	CH_2-c-C_3H_5		138–140[d]	*k*, *o*	88	$C_{21}H_{31}NO_5$	0.3 (0.2–0.5)	4.3 (2.2–11)
6	H	$CHMe_2$	CH_2-c-C_3H_5	B	92–93	*k*, *m*	65	$C_{17}H_{25}NO$	0.76 (0.53–1.1)	3.0 (1.9–5.3)
7	H	Bu	CH_2-c-C_3H_5	B	162–164 (0.4)	*h*	73	$C_{18}H_{27}NO$	2.2 (1.2–3.6)	5.6 (3.7–8.8)
8	H	CH_2CHMe_2	CH_2-c-C_3H_5	C	137–139[d]	*k*, *p*	91	$C_{22}H_{33}NO_5$	0.11 (0.08–0.15)	1.7 (1.2–3.4)
9	H	CH_2CHMe_2	CH_2-c-C_3H_5	E	127–128[d,e]	*k*, *p*		$C_{22}H_{33}NO_5$	0.06 (0.04–0.08)	1.1 (0.54–2.0)
10	H	CH_2CHMe_2	CH_2-c-C_3H_5	E	125–126[d,f]	*l*, *p*		$C_{22}H_{33}NO_5$	1.3 (0.84–2.8)	4.4 (2.4–57.0)
11[aa]	H	CHEtMe	CH_2-c-C_3H_5	A	155–158 (0.13)	*i*	*t*	$C_{18}H_{27}NO$	1.5 (0.77–2.5)	17 (6.0–62.0)
12	H	$(CH_2)_2CHMe_2$	CH_2-c-C_3H_5	A	167 (0.2)	*i*	62	$C_{19}H_{29}NO$	3.8 (1.8–7.7)	17 (1.8–70.0)
13[aa]	H	$CH_2CHEtMe$	CH_2-c-C_3H_5	A	169–170 (0.2)	*i*	53	$C_{19}H_{29}NO$[u]	2.8 (1.4–5.1)	>40
14	H	CH_2CMe_3	CH_2-c-C_3H_5	A	172–173 (0.5)	*i*	*t*	$C_{19}H_{29}NO$	0.19 (0.11–0.32)	3.3 (1.5–9.2)
15	H	CH_2-c-C_3H_5	CH_2-c-C_3H_5	A	175 (0.2)	*i*	*t*	$C_{18}H_{25}NO$[v]	4.9 (2.9–9.3)	1.3 (0.86–1.8)
16	H	Pr	c-C_3H_5	H	84	*j*, *q*	60	$C_{16}H_{23}NO \cdot 0.25H_2O$	16 (11.0–21)	~40
17	H	Pr	$(CH_2)_2$-c-C_3H_5	B	148–150 (0.2)	*h*	46	$C_{18}H_{27}NO$	14 (9.4–21)	4.9 (3.2–7.1)
18	H	Pr	CH_2-c-C_4H_7	A	154–158 (0.05)	*h*	75	$C_{18}H_{27}NO$	3.3 (1.1–13)	8.4 (2.9–5.1)
19	H	Pr	CH_2-c-C_5H_9	A	153–156 (0.02)	*h*	70	$C_{19}H_{29}NO$	33 (15–347)	>40
20	H	Pr	CH_2-c-C_6H_{11}	D	172–174 (0.35)	*i*	70	$C_{20}H_{31}NO$	>40	~40
21	H	Pr	CH_2-c-C_3H_4-1-Me	C	158–160 (0.3)	*h*	46	$C_{18}H_{27}NO$	4.0 (2.5–6.4)	~40
22[aa]	H	Pr	CH_2-c-C_3H_4-2-Me	C	150–151 (0.25)	*i*	73	$C_{18}H_{27}NO$	1.2 (0.51–2.3)	>40
23	COMe	Pr	CH_2-c-C_3H_5	F	139–143 (0.3)	*i*	77	$C_{19}H_{27}NO_2$[w]	0.4 (0.3–0.6)	8.2 (4.6–17)
24	COEt	Pr	CH_2-c-C_3H_5	F	155–158 (0.5)	*i*	43	$C_{20}H_{29}NO_2$	0.9 (0.77–1.3)	6.3 (4.1–9.6)
25	$CO(CH_2)_2Me$	Pr	CH_2-c-C_3H_5	G	170–171[g]	*j*, *r*	65	$C_{21}H_{32}ClNO_2$	0.86 (0.50–1.3)	9.1 (5.0–21)
26	$CO(CH_2)_3Me$	Pr	CH_2-c-C_3H_5	G	135–136[g]	*j*, *r*	23	$C_{22}H_{34}ClNO_2$	1.1 (0.60–1.8)	3.0 (1.8–4.8)
27	$CO(CH_2)_6Me$	Pr	CH_2-c-C_3H_5	G	114–115[g]	*j*, *n*	78	$C_{25}H_{40}ClNO_2$	2.5 (1.6–3.9)	10 (5.1–24)
28	$CO(CH_2)_8Me$	Pr	CH_2-c-C_3H_5	G	95–96[g]	*j*, *n*	58	$C_{27}H_{44}ClNO_2$	0.76 (0.38–1.7)	~40
29	$COCHMe_2$	Pr	CH_2-c-C_3H_5	G	168–170[g]	*j*, *r*	80	$C_{21}H_{32}ClNO_2$	0.23 (0.1–0.5)	7.1 (4.7–11)
30	COCHEtMe	Pr	CH_2-c-C_3H_5	G	165–166[g]	*j*, *r*	25	$C_{22}H_{34}ClNO_2 \cdot 0.5H_2O$	0.91 (0.57–1.5)	2.8 (1.9–4.2)
31	$COCH(Et)(CH_2)_3Me$ Pr		CH_2-c-C_3H_5	G	120–121[g]	*j*, *n*	62	$C_{25}H_{40}ClNO_2$	11 (6.1–33)	>40
32	$COCMe_3$	Pr	CH_2-c-C_3H_5	G	188–190[g]	*j*, *s*	55	$C_{22}H_{34}ClNO_2 \cdot 0.5H_2O$	0.91 (0.57–1.5)	7.5 (4.1–16)
33	COPh	Pr	CH_2-c-C_3H_5	G	102–106[g]	*j*, *s*	60	$C_{24}H_{30}ClNO_2$	1.7 (1.0–2.9)	~40
34	CO-c-C_3H_5	Pr	CH_2-c-C_3H_5	G	121[g]	*j*, *r*	53	$C_{21}H_{30}ClNO_2$	0.88 (0.56–1.4)	3.0 (0.73–8.5)
35	CO-c-C_4H_7	Pr	CH_2-c-C_3H_5	G	164–165[g]	*j*, *r*	65	$C_{22}H_{32}ClNO_2 \cdot 0.25H_2O$	1.2 (0.78–1.7)	8.7 (4.8–16)
36	CO-c-C_5H_9	Pr	CH_2-c-C_3H_5	G	167–169[g]	*j*, *r*	68	$C_{23}H_{34}ClNO_2 \cdot 0.5H_2O$	0.8 (0.47–1.3)	~40
37	$CH_2CH{=}CH_2$	Pr	CH_2-c-C_3H_5	I	152–155 (0.6)	*h*	37	$C_{20}H_{29}NO$[x]	8.9 (4.3–20)	24 (15–54)
Pentazocine[bb]									2.7 (1.75–4.0)	6.2 (2.8–11.9)

[a] Melting points are corrected and were determined in a capillary tube (using a Townson and Mercer, Ltd., apparatus). Boiling points are uncorrected. Compounds were not resolved into their optical isomers unless indicated by a footnote in this column. [b] Microanalyses for C, H, and N were within ±0.4% of the theoretical values except where otherwise indicated. [c] Crystallized as prisms, mp 89–90° (from aqueous EtOH). [d] Succinate salt prepared in $CHCl_3$. [e] (−) enantiomer, $[\alpha]^{25}D$ −14.1° (EtOH, *c* 0.993 g/100 ml). [f] (+) enantiomer, $[\alpha]^{25}D$ +14.1° (EtOH, *c* 0.957 g/100 ml). [g] Hydrochloride. [h] Oil. [i] Glass. [j] Microcrystalline. [k] Prisms. [l] Cubes. [m] Petroleum ether (bp 60–80°). [n] From C_6H_6–petroleum ether. [o] From ethyl methyl ketone. [p] From EtOH. [q] From aqueous EtOH. [r] From C_6H_6–cyclohexane. [s] From C_6H_6. [t] From crude intermediates. [u] C: calcd, 79.4; found, 79.9. Equivalent weight: calcd, 287.4; found, 287. [v] C: calcd, 79.7; found, 78.7. Equivalent weight: calcd, 271.4; found, 269. [w] C: calcd, 75.7; found, 75.25. [x] C: calcd, 80.2; found, 80.9. N: calcd, 4.7; found, 4.2. [y] The antinociceptive ED_{50} is the dose suppressing in 50% of T.O. strain mice the abdominal constriction response to intraperitoneal acetylcholine (3.2 mg/kg); 95% fiducial limits are indicated in parentheses. [z] The morphine antagonist ED_{50} is the dose suppressing in 50% of mice the antinociceptive effect of morphine (22.2 mg/kg subcutaneously) against the application of an artery clip to the base of the tail; 95% fiducial limits are indicated in parentheses. [aa] These compounds were tested as mixtures of isomers. [bb] References 1 and 8.

tive antimorphine dose (ED_{50}) of the test drug was that increasing to 50% the proportion of animals showing a nociceptive response after morphine with the test drug.

The ED_{50} values for antinociceptive activity and antimorphine activity for the various compounds are listed in Table I. Not less than ten mice were used at each dose level. Where the pyrrolidines were only available in the free-base form, aqueous solutions were prepared in the presence of 1 mol of D-tartaric acid.

Discussion

The use of mechanical tests for the evaluation of analgetics in animals has not proved a satisfactory procedure in the search for a nonaddicting drug of therapeutic value. A new era may be said to have started with the finding that certain compounds that are morphine antagonists, notably pentazocine, are effective analgesics in man.[11,12] The current use of pentazocine as an analgetic in medical practice, without classification as a narcotic, justifies an extensive examination of morphine antagonists.

The procedures described in this and other papers from these laboratories[1] have been devised to detect compounds that may well prove to be nonaddicting analgetics in man. The primary pharmacological properties of the compounds sought were a suitable antinociceptive potency as measured by the abdominal constriction test, together with the ability to antagonize the antinociceptive effects of morphine at a suitable dose level in the mouse. The results of these tests are given in Table I.

For the purpose of discussion, it is necessary to have some reference points to determine those compounds that are of particular interest. In the mouse abdominal constriction test, pentazocine has an ED_{50} of 2.7 mg/kg subcutaneously[8] and it therefore seems reasonable to exclude any compounds having an ED_{50} above 10 mg/kg subcutaneously as being unlikely to be clinically useful. Similarly, in the mouse antimorphine test, pentazocine has an ED_{50} of 6.2 mg/kg subcutaneously[1] and for the present purposes, it has been decided to exclude from discussion compounds with an ED_{50} above 10 mg/kg. Although these figures have been arbitarily decided, in fact, the compounds studied tended to fall into well-defined categories and borderline cases were rare; compounds that were suitably active in *both* tests were considered of potential interest.

Previous findings[3] with analgetics of the profadol type suggested that optimum antinociceptive activity was obtained with pyrrolidines substituted in the 3 position with both an *n*-propyl and a *m*-hydroxyphenyl group. The effects of substituting groups containing a cycloalkyl group on the nitrogen atom of *m*-(3-*n*-propyl-3-pyrrolidinyl)phenol were, therefore, examined. Reference to Table I (compounds **4**, **16**–**22**) shows that a cyclopropylmethyl substituent was the most effective in producing a suitable combination of both antinociceptive and antagonist properties (compound **4**). The only other N-substituent giving a compound which approached this in interest was the cyclobutylmethyl group (compound **18**), but its antinociceptive potency was only about one-eighth of that of compound **4**. The effect of using unsaturated alkyl groups as the nitrogen substituent will form the subject of a subsequent publication.[13]

The effect of substitution on the phenolic oxygen of *m*-[1-(cyclopropylmethyl)-3-*n*-propyl-3-pyrrolidinyl]phenol was then studied. In the profadol series, analogs in which the phenolic hydroxyl was replaced by methoxyl still showed a significant but smaller degree of antinociceptive activity.[14] In the present work, the methyl and allyl ethers (compounds **1** and **37**) had greatly reduced potencies in the abdominal constriction test and negligible activity as morphine antagonists.

On the other hand, in an extensive series of phenolic

esters, most have shown a degree of potency comparable with the parent phenol (compound 4) in the antinociceptive test. However, there was more variation in the antimorphine activity. In neither test was a clear relationship discernable between the structure of the acyl group and the biological activity. The unsubstituted 3-*m*-hydroxyphenyl seemed to be the aromatic substituent of choice for the pyrrolidine ring on the basis of these tests in mice but, studied in depth, the O esters might well offer potential advantages.

When unbranched 3-alkyl groups were varied, antinociceptive and antimorphine potencies diverged. In changing from methyl, to ethyl, to *n*-propyl, and to *n*-butyl (compounds **2**, **3**, **4**, and **7**), antinociceptive activity first rose sharply and then fell slightly between *n*-propyl and *n*-butyl, whereas morphine antagonism steadily fell. That antinociceptive and antimorphine activities diverged with increasing chain length in this series suggests that different receptors may be concerned with these two effects. Such a suggestion is consistent with the finding that tolerance to and dependence on morphine, nalorphine, and cyclazocine develop only in respect of their agonist (including antinociceptive) and not of their antagonist activity.[15,16] It also seems consistent with the biphasic dose–response curves obtained by various workers[17-19] for the analgetic activity of mixtures of narcotics and narcotic antagonists.

The effect of branching in the 3-alkyl substituent was also quite marked. In fact, the 3-isobutyl analog (compound **8**) produced the most potent antinociceptive compound of the racemates studied. 3-Isopropyl (compound **6**) and 3-neopentyl (compound **14**) also produced potent compounds, but the 3-*sec*-butyl (compound **11**) and other branched 3-pentyl analogs (compounds **12** and **13**) had greatly reduced activity. The antimorphine activity gave a similar rank order among these compounds. The explanation of these effects is not immediately apparent.

Finally, *m*-[1-(cyclopropylmethyl)-3-isobutylpyrrolidinly]phenol monosuccinate (compound **8**), the most potent racemate, has been prepared as its two optically active enantiomers. Although there was a significant difference in their potencies, both optical enantiomers showed antinociceptive activity. A similar effect was found in the antimorphine potencies. In contrast to the profadol series, however, where the (−) enantiomer was the more potent antinociceptive agent[3] and the (+) enantiomer the more potent in precipitating withdrawal symptoms in morphinized monkeys,‡ the (−) enantiomer of compounds **8** (compound **9**) proved to be more active in both the antinociceptive and the antimorphine tests. A more detailed account of compounds **8**–**10** is being prepared.[1]

Acknowledgments. The authors wish to thank Mr. F. H. Oliver for the microanalyses, Miss E. M. Tanner for the physical chemistry measurements, and Mrs. C. A. Dinneen for technical assistance with the pharmacological studies.

References

(1) R. E. Bowman, H. O. J. Collier, I. M. Lockhart, and C. Schneider, *Brit. J. Pharmacol.*, submitted for publication.
(2) I. M. Lockhart, British Patent 1,186,481 (1970).
(3) J. F. Cavalla, D. C. Bishop, R. A. Selway, N. E. Webb, C. V. Winder, and M. Welford, *J. Med. Chem.*, **8**, 316 (1965).
(4) I. M. Lockhart, N. E. Webb, M. Wright, C. V. Winder, and P. Varner, *ibid.*, **15**, 930 (1972).
(5) D. C. Bishop, J. F. Cavalla, I. M. Lockhart, M. Wright, C. V. Winder, A. Wong, and M. Stephens, *ibid.*, **11**, 466 (1968).
(6) J. F. Cavalla, I. M. Lockhart, N. E. Webb, C. V. Winder, M. Welford, and A. Wong, *ibid.*, **13**, 794 (1970).
(7) E. C. Horning and A. F. Finelli in "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, pp 790–791.
(8) H. O. J. Collier, L. C. Dinneen, C. A. Johnson, and C. Schneider, *Brit. J. Pharmacol. Chemother.*, **32**, 295 (1968).
(9) C. Bianchi and J. Franceschini, *ibid.*, **9**, 280 (1954).
(10) H. O. J. Collier in "Evaluation of Drug Activities: Pharmacometrics," D. R. Laurence and A. L. Bacharach, Ed., Academic Press, London, 1964, p 185.
(11) S. Archer, N. F. Albertson, L. S. Harris, A. K. Pierson, and J. G. Bird, *J. Med. Chem.*, **7**, 123 (1964).
(12) A. S. Keats and J. Telford, *J. Pharmacol. Exp. Ther.*, **143**, 157 (1964).
(13) R. E. Bowman, H. O. J. Collier, I. M. Lockhart, C. Schneider, N. E. Webb, and M. Wright, *J. Med. Chem.*, **16**, 1181 (1973).
(14) J. F. Cavalla, R. Jones, M. Welford, J. Wax, and C. V. Winder, *ibid.*, **7**, 412 (1964).
(15) D. R. Jasinski, W. R. Martin, and C. A. Haertzen, *J. Pharmacol. Exp. Ther.*, **157**, 420 (1967).
(16) W. R. Martin in "The Addictive States," A. Wickler, Ed., Williams and Wilkins, Baltimore, Md., 1968, pp 206–225.
(17) G. K. W. Yim, H. H. Keasling, E. G. Gross, and C. W. Mitchell, *J. Pharmacol. Exp. Ther.*, **115**, 96 (1955).
(18) R. W. Houde and S. L. Wallenstein, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **15**, 440 (1956).
(19) A. Rubin, H. I. Chernov, J. W. Miller, and G. J. Mannering, *J. Pharmacol. Exp. Ther.*, **144**, 346 (1964).

‡ J. E. Villarreal, private communication.