Convenient Synthesis of 6-Nor-9,10-dihydrolysergic Acid Methyl Ester

A. MICHAEL CRIDER *x, RICHARD GRUBB *, KENNETH A. BACHMANN *, and ARUN K. RAWAT ‡

Received January 22, 1981, from the **College of Pharmacy, University of Toledo, Toledo, OH 43606*, and the ‡*Alcohol Research Center, C.S. 10002, Toledo, OH 43699.* Accepted for publication April 8, 1981.

Abstract □ 6-Nor-9,10-dihydrolysergic acid methyl ester (IV) was prepared by demethylation of 9,10-dihydrolysergic acid methyl ester (II) with 2,2,2-trichloroethyl chloroformate, followed by reduction of the intermediate carbamate (III) with zinc in acetic acid. The 6-ethyl-V and 6-*n*-propyl-VI derivatives were prepared by alkylation of IV with the appropriate halide. All of the ergoline derivatives were evaluated for stereotyped behavior in rats, with 6-nor-6-ethyl-9,10-dihydrolysergic acid methyl ester (V) being active but much less potent than apomorphine. Compound VI was evaluated for its effect on blood pressure; at a dose of 30 mg/kg ip, it significantly lowered diastolic pressure in normotensive rats.

Keyphrases □ Ergolines—demethylation of the *N*-6 methyl group by 2,2,2-trichloroethyl chloroformate □ Derivatives—6-alkyl, of 6-nor-9,10-dihydrolysergic acid methyl ester □ Stereotyped behavior—ergolines, synthesis of 6-alkyl derivatives of 6-nor-9,10-dihydrolysergic acid methyl esters and evaluation in rats

Various compounds containing the ergoline (I) ring system are potent inhibitors of prolactin release (1–8). Ergolines appear to inhibit prolactin release by a dopaminergic mechanism (9). Due to their prolactin inhibitory activity, ergolines such as bromocriptine and lergotrile have demonstrated potential therapeutic value in the control of postpartum lactation and amenorrhea–galactorrhea associated with hyperprolactinemia. Additionally, these ergoline derivatives have potential in the treatment of parkinsonism (10).

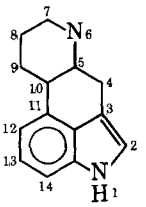
Replacement of the methyl group of I at position 6 by either ethyl or *n*-propyl groups increases prolactin inhibition (4, 6–7, 10). The most commonly employed method for demethylation of the *N*-6 methyl group of the ergoline system is a modification of the von Braun degradation (11), but an extremely poisonous cyanogen bromide is required in the reaction.

This paper reports a convenient synthesis of 6-nor-9,10-dihydrolysergic acid methyl ester (IV) utilizing 2,2,2-trichloroethyl chloroformate as the demethylating agent. The synthesis and pharmacological activity of the 6-ethyl-V and 6-*n*-propyl-VI derivatives of IV are also described.

RESULTS AND DISCUSSION

Chemistry—The synthesis of 6-nor-9,10-dihydrolysergic acid methyl ester (IV) was described previously (11). In this investigation, demethylation at position 6 of 9,10-dihydrolysergic acid methyl ester (II) was accomplished by modification of the von Braun degradation. The intermediate 6-nor-6-cyanoergoline was reduced by hydrogenation in the presence of Raney nickel to yield IV. The 6-nor-6-cyanoergolines have also been reduced to yield 6-nor-ergolines with sodium borohydride (12) and with zinc in acetic acid (13).

Several recent reports described the use of 2,2,2-trichloroethyl chloroformate to demethylate tertiary methylamines (14–16). The corresponding demethylated trichloroethyl carbamate derivatives are easily cleaved by reduction with zinc in acetic acid. In view of our present research program to synthesize 6-nor-6-alkylergolines as potential



I

dopaminergic agonists, the use of 2,2,2-trichloroethyl chloroformate as a demethylating agent was of interest.

Treatment of II with 2,2,2-trichloroethyl chloroformate in refluxing methylene chloride with potassium bicarbonate as the base afforded 6-nor-6-(2,2,2-trichloroethoxycarbonyl)-9,10-dihydrolysergic acid methyl ester (III) in a 90% yield. Reduction of the carbamate (III) with zinc in acetic acid at room temperature readily gave IV.

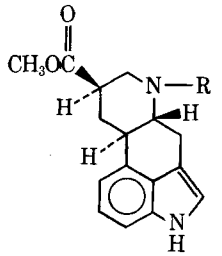
The 6-nor-6-ethyl-V and 6-nor-6-*n*-propyl-VI derivatives were prepared by alkylation of IV with an appropriate alkyl iodide in dimethylformamide with potassium carbonate as the base. Although the preparation of 6-nor-6-ethyl-9,10-(V) (11) and 6-nor-6-*n*-propyl-9,10-dihydrolysergic acid methyl ester (VI) (17) has been described, the biological activity of these compounds has not yet been reported.

The use of 2,2,2-trichloroethyl chloroformate represents a novel method for demethylation of the *N*-6-methyl group. The carbamate III is a potentially useful intermediate for the synthesis of potent dopaminergic ergolines such as pergolide (8).

Pharmacology—Of those ergolines examined for inducibility of behavioral stereotypy, only V exhibited any activity in doses up to 30 mg/kg. Not only was V less potent than apomorphine when behavior was ranked according to Costall *et al.* (18) (Fig. 1), but qualitative differences in behavior were also observed. For example, V elicited less gnawing behavior than apomorphine but produced intense salivation. The highest dose of V tested for activity (25 mg/kg) approached the lowest dose for which lethality was observed (30 mg/kg). Death appeared due to respiratory arrest and was sometimes preceded by clonic seizures.

Table I lists the mean activity per rat. The activities for apomorphine and V are depicted in Figs. 1 and 2 and are expressed as a percentage of the maximum activity observed. The ratios of killed per treated rats are given in Table II.

During the tests for behavioral stereotypy, both II and VI were noted to elicit flushing of the tail, ears, and paws. This effect was especially pronounced and reproducible for VI and occasioned the analysis of VI on blood pressure. Compound VI did not significantly alter systolic pressure, but single intraperitoneal doses (30 mg/kg) significantly lowered



II: R = CH_3
III: R = $CO_2CH_2CCl_3$
IV: R = H
V: R = CH_2CH_3
VI: R = $CH_2CH_2CH_3$

0022-3549/81/1200-1319$01.00/0

Table I—Induction of Behavioral Stereotypes [a] in Rats

Compound	Dose[b], mg/kg	*n*	Mean Activity/Rat
Controls[c]	1	6	0
Apomorphine	10	15	12.7
II	30	4	0.25
III	30	4	0
V	3	4	0.25
	6	4	1.0
	9	4	1.25
	15	4	2.25
	20	4	3.5
	25	4	5.25
VI	30	3	0.33

[a] Stereotypic behavior was scored according to the scale of Costall *et al.* (18). [b] All compounds were administered intraperitoneally in polyethylene glycol 400 (70%). [c] Controls received polyethylene glycol 400 (1 ml/kg).

diastolic pressure in normotensive rats (Fig. 3). The hypotensive effect of VI occurred at 2 hr and was sustained for 1 hr. The hypotensive effects of VI relative to polyethylene glycol 400 (PEG) may have been obscured by an apparently abrupt (although statistically insignificant) increase in diastolic pressure (Fig. 3).

Hypotensive activity with certain ergolinyl methyl esters was reported previously (19, 20).

EXPERIMENTAL[1]

6-Nor-6-(2,2,2 - trichloroethoxycarbonyl)-9,10-dihydrolysergic Acid Methyl Ester (III)—A mixture of II (21) (0.425 g, 0.0015 mole), potassium bicarbonate (0.729 g, 0.0073 mole), and 2,2,2-trichloroethyl chloroformate (0.619 g, 0.0029 mole) in 60 ml of absolute methylene chloride was refluxed for 24 hr. 2,2,2-Trichloroethyl chloroformate (1.48 g, 0.0070 mole) was added, and refluxing was continued for an additional 24 hr. The reaction mixture was cooled, filtered, and evaporated under reduced pressure to yield a white solid. Recrystallization from absolute methanol gave 0.602 g (90%) of crystalline product, mp 208–210°; IR (KBr): 3485 (N–H, indole) and 1740 (C=O, ester and carbamate) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 3.70 (s, 3H, $COOCH_3$), 4.90 (s, 2H, OCH_2CCl_3), 6.67–7.20 (m, 4H, aromatic), and 7.27 (s, 1H, NH).

Anal.—Calc. for $C_{19}H_{19}Cl_3N_2O_4$: C, 51.19; H, 4.30; Cl, 23.86; N, 6.29. Found: C, 51.14; H, 4.20; Cl, 24.21; N, 6.13.

6-Nor-9,10-dihydrolysergic Acid Methyl Ester (IV)—A solution of III (0.877 g, 0.0020 mole) in 100 ml of acetic acid was treated in one portion with powdered zinc dust (2.58 g, 0.039 g-atom), and the mixture was stirred for 60 hr at room temperature. Then the reaction mixture was filtered, and the inorganic residue was washed with acetic acid. The reaction mixture was diluted with water (100 ml) and extracted two times

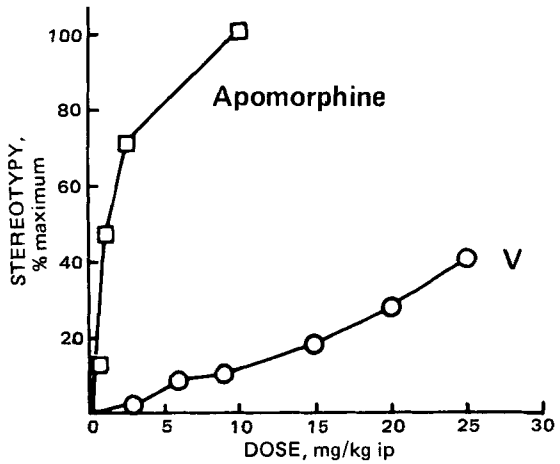


Figure 1—*Dose–response curves for stereotypic behavior induced by apomorphine (□) or V (○).*

[1] Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. IR spectra were recorded as potassium bromide pellets with a Perkin-Elmer 137 spectrophotometer. NMR spectra were recorded on a Varian EM 360A spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (1%) as the internal standard. Analytical data were obtained from Micro-Analysis Inc., Wilmington, Del.

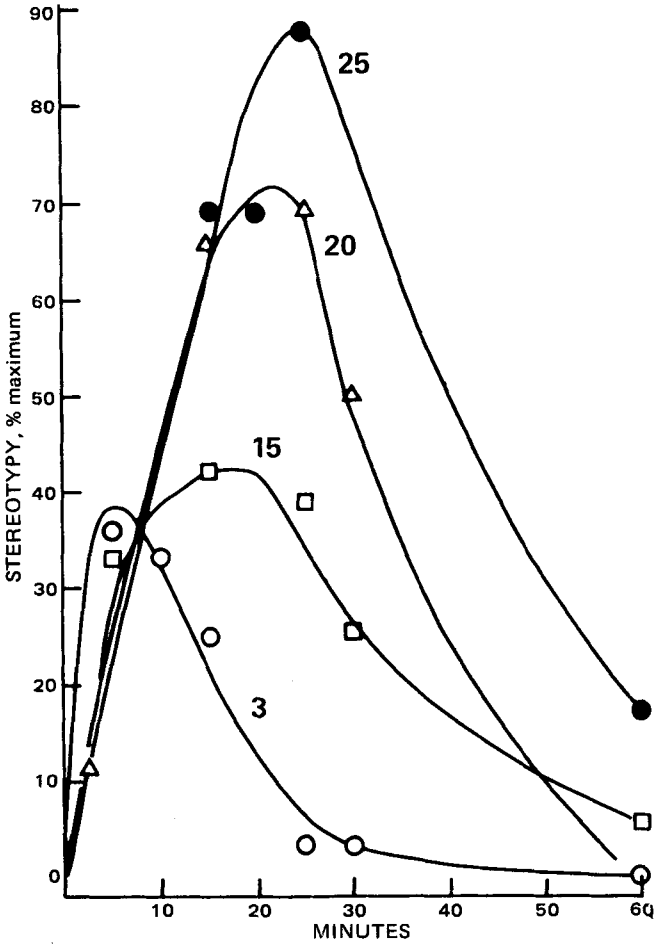


Figure 2—*Time course of stereotypic behavior induced by graded doses of V. Numbers denote doses of V (milligrams per kilogram).*

with 50-ml portions of chloroform. The aqueous acetic acid solution was cooled in an ice bath and carefully basified with 8 *N* NH_4OH solution.

The basic solution was extracted three times with 75-ml portions of chloroform. The combined chloroform extracts were dried (sodium sulfate), filtered, and evaporated under reduced pressure to yield 0.384 g (72%) of a light-tan solid. The hydrogen maleate salt was prepared and recrystallized from methanol to yield analytically pure material, mp 211–213° [lit. (11) mp of the free base 172°]; IR (KBr): 3300 (N–H, indole) and 1700 (C=O, ester) cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 3.70 (s, 3H, $COOCH_3$), 7.10 (s, 1H, NH), and 6.50–7.17 (m, 4H, aromatic).

Anal.—Calc. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.75; N, 7.25. Found: C, 62.20; H, 5.88; N, 7.04.

6-Nor-6-*n*-propyl-9,10-dihydrolysergic Acid Methyl Ester (VI)—A mixture of IV (0.300 g, 0.0011 mole) and potassium carbonate (0.306 g, 0.0022 mole) in 25 ml of dimethylformamide was treated with *n*-propyl iodide (0.377 g, 0.0022 mole). After heating for 24 hr at 50°, the reaction mixture was cooled, filtered, and evaporated under reduced pressure to afford a light-brown oil. The oil was taken up into 200 ml of chloroform and washed with 200 ml of water. The chloroform phase was dried (sodium sulfate), filtered, and concentrated under reduced pressure to give a light-tan solid. Recrystallization from methanol afforded, in two crops, 0.162 g (47%) of analytically pure material, mp 215–216° [lit. (17) 212–214°]; IR (KBr): 3300 (N–H, indole) and 1730 (C=O, ester) cm^{-1}; NMR

Table II—Lethality of V

Dose, mg/kg	Dead/Treated
20	0/4
25	0/4
30	1/4
40	1/4
50	2/4

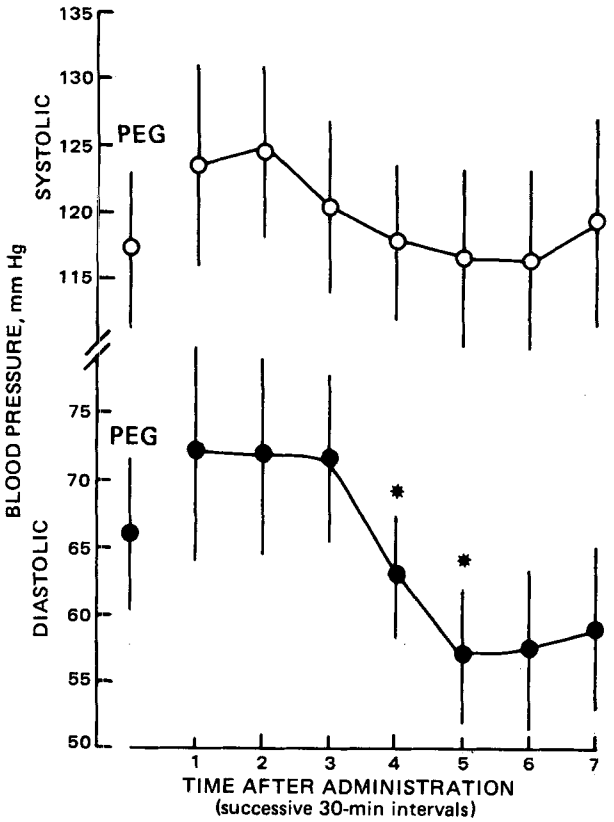


Figure 3—*Impact of VI on blood pressure. Vertical bars denote standard error of the mean (n = 4), and asterisk signifies* $p < 0.05$.

($CDCl_3$): δ 0.90 (t, 3H, $CH_2CH_2CH_3$), 1.07–3.53 (m, 13H), 3.70 (s, 3H, $COOCH_3$), 6.87–7.23 (m, 4H, aromatic), and 7.97 (s, 1H, NH).

Anal.—Calc. for $C_{19}H_{24}N_2O_2$: C, 73.02; H, 7.76; N, 8.97. Found: C, 73.04; H, 7.59; N, 8.94.

6-Nor-6-ethyl-9,10-dihydrolysergic Acid Methyl Ester (V)—This compound was synthesized from IV (0.202 g, 0.0008 mole), potassium carbonate (0.103 g, 0.0008 mole), and ethyl iodide (0.233 g, 0.0015 mole) in 25 ml of dimethylformamide in the same manner as described for VI. Column chromatography of the product with silica gel as the adsorbent and chloroform–methanol (95:5) as the solvent, gave, after evaporation of the solvents, 0.162 g (75%) of a light-brown solid, mp 168–169° [lit. (11) 170–174°]; IR (KBr): 3300 (N–H, indole) and 1730 (C=O, ester) cm^{-1}.

Pharmacological Testing—Ergolines II, III, V, and VI were evaluated for their ability to induce stereotypic behavior in rats. Stereotyped behavior was scored with the system of Costall *et al.* (18). Male Sprague–Dawley rats[2] were given intraperitoneal injections of test substances dissolved in polyethylene glycol 400 (70%). Dosages are listed in Table I. Apomorphine was used as a reference compound, and control animals received only polyethylene glycol 400 (1 ml/kg). Observations were made for 6 hr while animals were housed individually in clear, polycarbonate cages (25.4 × 46.4 × 20.3 cm).

The time course of V after single intraperitoneal doses was evaluated using a slightly different scoring system. Animals were accorded points graded for intensity as follows: no activity, 0; sniffing, 1, 2, or 3; licking, 4, 5, or 6; and gnawing, 7, 8, or 9. Figure 2 shows the time course for V following doses of 3, 9, 15, 20, and 25 mg/kg. Activity is expressed as a percentage of the maximum observed.

Blood pressure was recorded directly from the carotid artery. Heparinized rats were anesthetized with urethan (1.2 g/kg ip). Polyethylene cannula tubing[3] (0.58-mm i.d., 0.97-mm o.d.) was inserted into the carotid artery and connected *via* a three-way valve to a pressure transducer[4]. Recordings were made with a physiological recorder[5]. The system was calibrated prior to recording blood pressure for each animal. Both systolic and diastolic pressures were recorded continuously.

Each animal served as its own control, receiving polyethylene glycol 400 initially, followed by VI at a dose of 30 mg/kg. All injections were given intraperitoneally. Animals were allowed to stabilize for 60 min after injection of polyethylene glycol 400 and prior to the injection of VI dissolved in polyethylene glycol 400 (*vide supra*). Pressures for each animal for the control (polyethylene glycol 400) interval and for each successive 30-min interval after treatment with VI represent average pressures ($n = 7$) for the interval (Fig. 3). Pressure differences between polyethylene glycol 400 treatment and treatment with VI were evaluated for significance using the paired rank sum test of Wilcoxon (22).

The acute toxicity of V was determined by noting the number of animals surviving 24 hr after administration.

[2] Harland.
[3] Intramedic.
[4] Statham P23AA.
[5] Beckman Type R411 dynograph.

REFERENCES

(1) H. G. Floss, J. M. Cassady, and J. E. Robbers, *J. Pharm. Sci.*, **62,** 699 (1973).

(2) J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Med. Chem.*, **17,** 300 (1974).

(3) G. S. Li, J. M. Robinson, H. G. Floss, J. M. Cassady, and J. A. Clemens, *ibid.*, **18,** 892 (1975).

(4) A. M. Crider, J. M. Robinson, H. G. Floss, J. M. Cassady, and J. A. Clemens, *ibid.*, **20,** 1473 (1977).

(5) P. L. Stutz, P. A. Stadler, J. M. Vigouret, and A. Jaton, *ibid.*, **21,** 754 (1978).

(6) A. Cerny, J. Krepelka, and M. Semonsky, *Collect. Czech. Chem. Commun.*, **44,** 946 (1979).

(7) M. Beran, J. Krepelka, and M. Semonsky, *ibid.*, **44,** 3385 (1979).

(8) R. W. Fuller, J. A. Clemens, E. C. Kornfeld, H. D. Snoddy, E. B. Smalstig, and N. J. Bach, *Life Sci.*, **24,** 375 (1979).

(9) J. A. Clemens, E. B. Smalstig, and C. J. Shaar, *Acta Endocrinol.*, **79,** 230 (1975).

(10) N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.*, **23,** 481 (1980), and references cited therein.

(11) T. Fehr, P. A. Stadler, and A. Hofmann, *Helv. Chim. Acta*, **53,** 2197 (1970).

(12) V. Prelog, B. C. Musick, J. R. Merchant, S. Julia, and M. Wilhelm, *ibid.*, **39,** 498 (1956).

(13) E. C. Kornfeld and N. J. Bach, U. S. pat. 4,166,182 (1979).

(14) T. A. Montzka, J. D. Matiskella, and R. A. Partyka, *Tetrahedron Lett.*, **1974,** 1325.

(15) R. F. Borne, J. A. Bedford, J. L. Buelke, C. B. Craig, T. C. Hardin, A. H. Kibbee, and M. C. Wilson, *J. Pharm. Sci.*, **66,** 119 (1977).

(16) J. R. Pfister, *J. Org. Chem.*, **43,** 4373 (1978).

(17) J. Krepelka, A. Cerny, R. Kotva, and M. Semonsky, *Collect. Czech. Chem. Commun.*, **42,** 1209 (1977).

(18) B. Costall, R. J. Naylor, and J. E. Olley, *Eur. J. Pharmacol.*, **18,** 83 (1972).

(19) M. Beran, J. Krepelka, K. Rezabek, M. Seda, and M. Semonsky, *Collect. Czech. Chem. Commun.*, **42,** 1407 (1977).

(20) J. Krepelka, M. Beran, K. Rezabek, V. Trcka, and M. Semonsky, Czechoslovakian pat. 171, 570 (1978); through *Chem. Abstr.*, **90,** 39102t (1979).

(21) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **106,** 393 (1934).

(22) R. G. Steele and J. H. Torrie, "Principles and Procedures of Statistics," McGraw-Hill, New York, N.Y., 1960, p. 402.

ACKNOWLEDGMENTS

Supported by a faculty research award from the University of Toledo Faculty Research Awards and Fellowships Program.

The authors thank Dr. Fedrico Arcamone at Farmitalia Research Institute for a generous supply of dihydrolysergic acid.