3-Halo-2-phenylglycidamide Hypnotics

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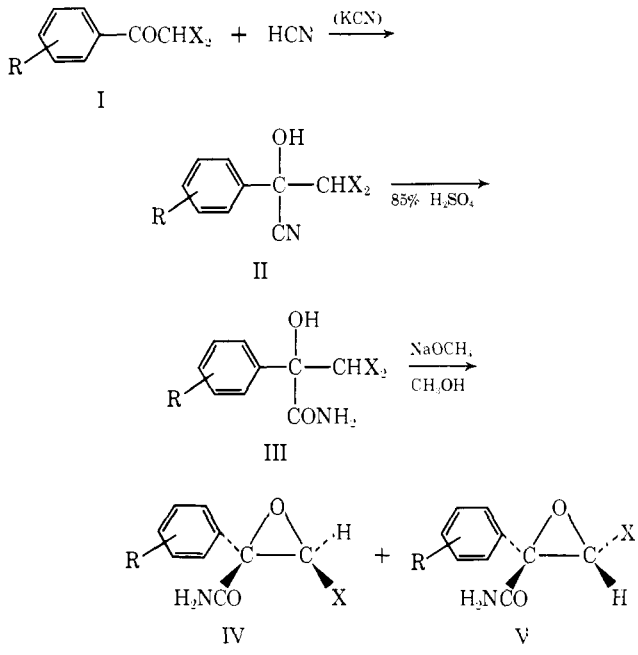
A series of 3-halo-2-phenylglycidamides has been synthesized and evaluated as hypnotics in mice. 3-Chloro-2-(2,4-dichlorophenyl)glycidamide (**54**) was found to be equal in hypnotic potency to sodium pentobarbital and to have a fourfold greater therapeutic ratio.

Some glycidamides are known to be central nervous system depressants. Several 2,3-dialkyl- and 3,3-dialkylglycidamides have been reported in a review by Wheeler[1] on nonbarbiturate hypnotics. The 2-ethyl-3-propylglycidamide, oxanamide, is marketed as a minor tranquilizer. Although a few 2-phenyl-3-alkylglycidamides are known,[2,3] they have not been reported to possess hypnotic activity. This paper deals with the synthesis and pharmacology of the 3-halo-2-phenylglycidamides, a heretofore unreported class of compounds.

Chemistry.—Isomer mixtures of the 3-halo-2-phenylglycidamides (IV and V) were prepared in good over-all yield from 2,2-dihaloacetophenones (I) as shown in Scheme I. Two methods were employed to obtain the

SCHEME I



starting 2-haloacetophenones. Friedel–Crafts acylation of the appropriately substituted benzene with chloro- or dichloroacetyl chloride afforded 60–90% yields of the corresponding 2-chlorinated acetophenones. Acylation of mixed halogenated benzenes has been reported[4] to afford isomeric mixtures in which the isomer resulting from acylation *para* to the most electronegative halogen predominates. Acylation of *m*-chlorofluorobenzene with dichloroacetyl chloride afforded a mixture consisting of approximately 60% of 2,2,2′-trichloro-4′-fluoroacetophenone. From this mixture 2,2,2′-trichloro-4′-fluoroacetophenone was isolated in 10% yield. Similarly, acylation of *m*-chlorotoluene gave a crude mixture consisting of approximately 40% of 2,2,4′-trichloro-2′-methylacetophenone, 50% of 2,2,2′-trichloro-4′-methylacetophenone, and 10% of unidentified material as determined by glpc. The two major components were isolated in 15% yields by distillation.

Chlorination at the 2 position of the appropriately ring-substituted acetophenone was effected in 90–100% yields by the method of Falbe and Schulze-Steinen.[5] 2,2-Dibromo-2′,4′-dichloroacetophenone was obtained by this method using Br_2 at 65–70°. In ring-deactivated acetophenones the reaction proceeds smoothly to afford 2,2-dihaloacetophenones; however, in activated acetophenones ring chlorination can occur. With 3 moles of chlorine/mole of 4′-methoxyacetophenone the product was 2,2,3′-trichloro-4′-methoxyacetophenone.

HCN reacts readily with I to afford the corresponding mandelonitriles (II). The mandelonitriles prepared, their method of synthesis and yields are summarized in Table I. In general, better yields of II, 65–100%, were obtained when liquid HCN was used as a solvent to afford a homogeneous reaction mixture.[6] Difficulty was encountered in obtaining analytically pure samples of II due to the tendency of the cyanohydrin formation to reverse. Therefore, most of the mandelonitriles were converted to the corresponding mandelamides (III) (Table II) without extensive purification.

In general, the mandelamides containing halogens on the α-methyl group and electron-withdrawing substituents on the phenyl ring were obtained in better than 50% yield without exhaustive work-up. The low yield of **30** (42%) and of **32** (18%) might be explained on the basis of steric hindrance to hydrolysis of the CN group by the bulky α-trichloromethyl and α-dibromomethyl groups. Noticeably lower yields were also obtained from mandelonitriles containing electron-donating groups on the phenyl ring, **27** and **41**. In the prepara-

(1) K. W. Wheeler, "Medicinal Chemistry," Vol. VI, E. E. Campaigne and W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 110.

(2) E. C. Knowles and J. B. Cloke, *J. Am. Chem. Soc.*, **54**, 2028 (1932).

(3) J. V. Murray and J. B. Cloke, *ibid.*, **56**, 2749 (1934).

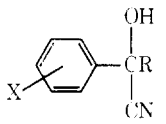
(4) B. K. Diep, N. P. Buu-Hoi, and N. D. Xuong, *J. Chem. Soc.*, 2784 (1963).

(5) J. Falbe and H. J. Schulze-Steinen, German Patent 1,223,284 (1966).

(6) Caution should be exercised when carrying out this reaction on a large scale in liquid hydrogen cyanide with 2-chloro- or 2,2-dichloroacetophenones. The reaction proceeds instaneously upon addition of the catalyst. The evolution of large amounts of heat causes vigorous boiling of the hydrogen cyanide.

TABLE I

MANDELONITRILES



No.	X	R	Method[a]	Yield, %	Mp, °C
1	H	$CHCl_2$	L	86	60–63
2	2-Cl	$CHCl_2$	L	87	74.5–81
3	4-Cl	$CHCl_2$	L	100	Crude liquid
4	4-Br	$CHCl_2$	L	98	Crude liquid
5	4-F	$CHCl_2$	L	100	Crude liquid
6	4-CH_3	$CHCl_2$	L	100	Crude liquid
7	4-CH_3SO_2	$CHCl_2$	L	100	162–164
8	2,4-Cl_2	$CHCl_2$	L	84	93–95
9	2,4-Cl_2	CCl_3	C	67	122–126
10	2,4-Cl_2	CH_2Cl	L	95	81–83
11	2,4-Cl_2	$CHBr_2$	L	95	Crude liquid
12	2,5-Cl_2	$CHCl_2$	L	65	125–126.5
13	2,5-Cl_2	CH_2Cl	L	90	106.5–107.5
14	2,4,5-Cl_3	$CHCl_2$	L	93	123–127
15	2,3,4-Cl_3	$CHCl_2$	C	77	133–140
16	2-Cl, 4-F	$CHCl_2$	C	83	96–98
17	2-Cl, 4-CH_3	$CHCl_2$	L	100	Crude liquid
18	2-CH_3, 4-Cl	$CHCl_2$	L	91	93–100
19	2,4-F_2	$CHCl_2$	C	67	63–66
20	3-Cl, 4-CH_3O	$CHCl_2$	L	86	93–98
21	3-NO_2	CH_2Cl	L	86	111–114

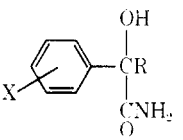
[a] L, liquid HCN obtained from a cylinder; C, HCN generated *in situ*.

were converted smoothly by either NaOMe or NaH to the corresponding 2-phenylglycidamides (Table III). With the α-dichloromethylmandelamides, NaOMe is preferable to NaH due to higher yields and a cleaner, more easily controlled reaction. With the α-chloromethylmandelamides NaH was the base utilized since MeO^- can effect reopening of the epoxide ring. Kerriman and coworkers[7] have reported a similar ring closure of 2,2-dichloro-2-phenylethanol with NaH to afford α-chlorostyrene oxide. Two isomeric glycidamides, IV and V, were obtained from the α-dichloromethylmandelamides. The isomers were arbitrarily designated as A and B on the basis of the ratio of isomers obtained, their chromatographic retention time, and stability. In each isomeric pair the major component, designated B, had a longer chromatographic retention time on silica gel G. Certain isomers of the A designation, lacking a 2 substituent on the phenyl ring, decomposed upon standing to polymerlike materials with the evolution of HCl.

The configurations have been assigned on the basis of steric factors controlling the induction of a second asymmetric center adjacent to an existing asymmetric center. Since epoxide formation from halohydrins is known to proceed by an intramolecular S_N2 reaction involving backside attack of the oxygen anion on the halogen-bearing carbon,[8] the OH and leaving Cl must exist in the *trans* configuration. In the dichloromethylmandelamides two conformations exist in which reaction can

TABLE II

MANDELAMIDES



No.	X	R	Yield, %	Mp, °C	Formula	Analyses
22	H	$CHCl_2$	77	148.5–150.5	$C_9H_8Cl_2NO_2$	N, Cl
23	2-Cl	$CHCl_2$	83	157.5–165	$C_9H_7Cl_3NO_2$	N; Cl[b]
24	4-Cl	$CHCl_2$	67	153–157	$C_9H_7Cl_3NO_2$	N, Cl
25	4-Br	$CHCl_2$	43	174–177	$C_9H_7BrCl_2NO_2$	N[c]
26	4-F	$CHCl_2$	67	154.5–157	$C_9H_7Cl_2FNO_2$	N, Cl
27	4-CH_3	$CHCl_2$	35	73–76	$C_{10}H_{11}Cl_2NO_2$	N; Cl[d]
28	4-CH_3SO_2	$CHCl_2$	83	208–212	$C_{10}H_{11}Cl_2NO_4S$	N, Cl
29	2,4-Cl_2	$CHCl_2$	81	135–137	$C_9H_7Cl_4NO_2$	N, Cl
30	2,4-Cl_2	CCl_3	42	154–156.5	$C_9H_6Cl_5NO_2$	N; Cl[e]
31	2,4-Cl_2	CH_2Cl	72	136–137	$C_9H_8Cl_3NO_2$	N, Cl
32	2,4-Cl_2	$CHBr_2$	18	125–128.5	$C_9H_7Br_2Cl_2NO_2$	N[c]
33	2,5-Cl_2	$CHCl_2$	94	148–152	$C_9H_7Cl_4NO_2$	N, Cl
34	2,5-Cl_2	CH_2Cl	97	151.5–156	$C_9H_8Cl_3NO_2$	N; Cl[f]
35	2,4,5-Cl_3	$CHCl_2$	77	125.5–130.5	$C_9H_6Cl_5NO_2$	N; Cl[g]
36	2,3,4-Cl_3	$CHCl_2$	74	134–137	$C_9H_6Cl_5NO_2$	N, Cl
37	2-Cl, 4-F	$CHCl_2$	53	126–127	$C_9H_7Cl_3FNO_2$	N, Cl
38	2-Cl, 4-CH_3	$CHCl_2$	50[h]	139–141	$C_{10}H_{10}Cl_3NO_2$	N, Cl
39	2-CH_3, 4-Cl	$CHCl_2$	50	130.5–132.5	$C_{10}H_{10}Cl_3NO_2$	N, Cl
40	2,4-F_2	$CHCl_2$	68	128–130	$C_9H_7Cl_2F_2NO_2$	N, Cl
41	3-Cl, 4-CH_3O	$CHCl_2$	19	155.5–158.5	$C_{10}H_{10}Cl_3NO_3$	N, Cl
42	3-NO_2	CH_2Cl	87	178–181	$C_9H_8ClN_2O_4$	N, Cl

[a] Cl: calcd, 39.6; found, 38.8. [b] Halogen equiv: calcd, 101; found, 103. [c] Cl: calcd, 28.6; found, 31.6. [d] Cl: calcd, 52.6; found, 52.1. [e] Halogen equiv: calcd, 98; found, 98. [f] Cl: calcd, 39.6; found, 38.5. [g] Cl: calcd, 52.6; found, 52.1. [h] Based on the acetophenone starting material.

tion of **41**, cleavage of MeO also occurred to afford as the major product a 23% yield of the corresponding phenolic mandelamide.

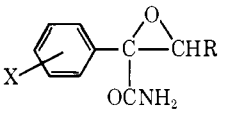
The α-chloro- or α-dichloromethylmandelamides (III) occur, one leading to a transition-state eclipsing of H

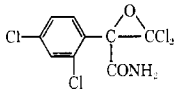
(7) A. Kerriman, P. Duhamel, and M. R. Neuri Bi Morghi, *Bull. Soc. Chim. France*, 3264 (1964).

(8) S. Winstein and H. J. Lucas, *J. Am. Chem. Soc.*, **61**, 1576 (1939).

Table III

2-Phenylglycidamides



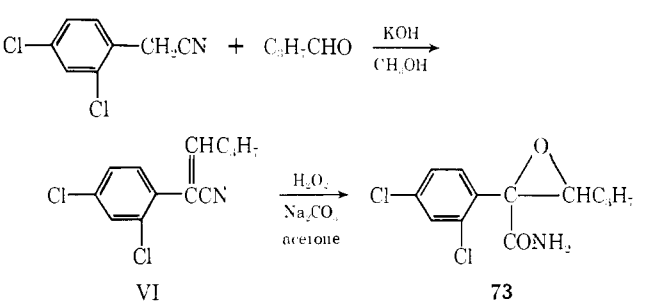
No.	X	R	Isomer	Yield, %	Mp, °C	Formula	Analyses
43	H	Cl	B[a,b]	36	67–77	$C_9H_8ClNO_2$	N, Cl
44	H	Cl	A	3	113–114	$C_9H_8ClNO_2$	N, Cl
45	2-Cl	Cl	B	40	101–104	$C_9H_7Cl_2NO_2$	N; Cl[c]
46	2-Cl	Cl	A	1	165–168.5	$C_9H_7Cl_2NO_2$	N; Cl[d]
47	4-Cl	Cl	B	34	90.5–94	$C_9H_7Cl_2NO_2$	N; Cl[e]
48	4-Cl	Cl	B[b]	16	112.5–113	$C_9H_7Cl_2NO_2$	N; Cl[f]
49	4-Br	Cl	B	34	108–109.5	$C_9H_7BrClNO_2$	N[g]
50	4-Br	Cl	A[b]	23	102.5–104	$C_9H_7BrClNO_2$	N[h]
51	4-F	Cl	B[i]	13	113–117	$C_9H_7ClFNO_2$	N, Cl
52	4-CH_3	Cl	B[i]	15	157–158.5	$C_{10}H_{10}ClNO_2$	N, Cl[j]
53	4-CH_3SO_2	Cl	B[i]	27	156–158.5	$C_{10}H_{10}ClNO_4S$	N; Cl[k]
54	2,4-Cl_2	Cl	B	64	122.5–124	$C_9H_6Cl_3NO_2$	N, Cl
55	2,4-Cl_2	Cl	A	3	170–171.5	$C_9H_6Cl_3NO_2$	N, Cl
56	2,4-Cl_2	H		76	124–127	$C_9H_7Cl_2NO_2$	N, Cl
57	2,4-Cl_2	Br	B[i]	69	139–140.5	$C_9H_6BrCl_2NO_2$	N[l]
58	2,5-Cl_2	Cl	B	59	160–162	$C_9H_6Cl_3NO_2$	N, Cl
59	2,5-Cl_2	Cl	A	7	175.5–177	$C_9H_6Cl_3NO_2$	N; Cl[m]
60	2,5-Cl_2	H		72	186.5–190	$C_9H_7Cl_2NO_2$	N; Cl[n]
61	2,4,5-Cl_3	Cl	B	73	131.5–135	$C_9H_5Cl_4NO_2$	N, Cl
62	2,4,5-Cl_3	Cl	A	4	162.5–166	$C_9H_5Cl_4NO_2$	N; Cl[o]
63	2,3,4-Cl_3	Cl	B	68	141.5–143	$C_9H_5Cl_4NO_2$	N, Cl
64	2,3,4-Cl_3	Cl	A	1	192	$C_9H_5Cl_4NO_2$	N, Cl
65	2-Cl, 4-F	Cl	B	50	96–102	$C_9H_6Cl_2FNO_2$	N, Cl
66	2-Cl, 4-F	Cl	A	2	168–170	$C_9H_6Cl_2FNO_2$	N, Cl
67	2-Cl, 4-CH_3	Cl	B	59	98.5–100.5	$C_{10}H_9Cl_2NO_2$	N, Cl
68	2-Cl, 4-CH_3	Cl	A	2	140–141.5	$C_{10}H_9Cl_2NO_2$	N; Cl[p]
69	2-CH_3, 4-Cl	Cl	B	72	96–99	$C_{10}H_9Cl_2NO_2$	N, Cl
70	2-CH_3, 4-Cl	Cl	A	4	112.5–114.5	$C_{10}H_9Cl_2NO_2$	N
71	2,4-F_2	Cl	B[i]	19	98–99	$C_9H_6ClF_2NO_2$	N, Cl
72	3-NO_2	H		35	109.5–112.5	$C_9H_8N_2O_4$	N
73	2,4-Cl_2	C_3H_7	*q*	73	161–162	$C_{12}H_{13}Cl_2NO_2$	N, H; C[r]
74				16	106–106.5	$C_9H_5Cl_4NO_2$	N, Cl

[a] 85% B isomer, 15% A isomer by nmr. [b] Decomposed upon standing. [c] Cl: calcd, 30.5; found, 31.0. [d] Cl: calcd, 30.5; found, 31.0. [e] Cl: calcd, 30.5; found, 31.8. [f] Cl: calcd, 30.5; found, 31.8. [g] Halogen equiv: calcd, 138; found, 134. [h] Halogen equiv: calcd, 138; found, 134. [i] Pure A isomer was not isolated. [j] N: calcd, 6.6; found, 7.3. Cl: calcd, 16.8; found, 19.0. [k] Cl: calcd, 12.9; found, 13.5. [l] Halogen equiv: calcd, 103; found, 103. [m] Cl: calcd, 39.9; found, 40.6. [n] Cl: calcd, 30.6; found, 29.1. [o] Cl: calcd, 47.2; found, 48.1. [p] N: calcd, 5.7; found, 5.0. Cl: calcd, 28.8; found, 32.0. [q] Isomer form uncertain, see text. [r] C: calcd, 52.5; found, 53.4.

with the phenyl ring and the other to eclipsing of Cl with the phenyl ring. Since the steric requirement of Cl exceeds that of H, less steric hindrance to eclipsing, and, therefore, a lower transition-state energy would be expected to occur in the conformation leading to the product in which the phenyl ring and α-H are *cis*. On this basis the predominant B isomer has been assigned configuration IV, that having the phenyl and the Cl *trans* on the epoxide ring. This assignment is supported by the higher B/A isomer ratio obtained with glycidamides having greater steric requirements due to an *ortho* substituent on the phenyl ring as compared to those lacking an *ortho* substituent. The α-dichloromethylmandelamides with an *ortho* substituent on the phenyl ring give isomeric mixtures consisting of 85–95% B isomer and 5–15% A isomer. In contrast, mixtures of approximately 60% B and 40% A were formed from the α-dichloromethylmandelamides lacking an *ortho* substituent on the phenyl ring.

2-(2,4-Dichlorophenyl)-3-propylglycidamide (**73**) was prepared in 73% yield by the alkaline peroxide oxidation[2] of 2-(2,4-dichlorophenyl)-2-hexenenitrile (VI) as shown in Scheme II. VI was obtained by the base-

Scheme II



VI 73

catalyzed condensation[9] of 2,4-dichlorobenzyl cyanide and butyraldehyde. The configuration of **73** cannot be assigned unequivocally since the stereochemical course

(9) A. Vigier and J. Dreux, *Bull. Soc. Chim. France*, 677 (1963).

of the alkaline peroxide oxidation has not been studied. Assuming the thermodynamically most stable isomer of VI would have Ph and Pr *trans*, **73** is thought to be of the B configuration.

Pharmacologic Methods.—With the exception of **48**, which decomposed upon standing, the 2-phenylglycidamides in Table III have been tested in mice for hypnotic activity. Each chemical was administered intraperitoneally to groups of ten male albino mice (23–27 g) individually housed. Loss of the righting reflex for 1 min was considered a positive response. Termination of hypnosis was judged by a persistent righting response. Compounds producing a positive response at 180 mg/kg were considered active.

Pharmacological Results and Discussion.—The HD_{50} and LD_{50} dose levels of the active compounds, calculated by the moving average method of Thompson[10] or the method of Litchfield and Wilcoxon,[11] are summarized in Table IV. In general, rigid steric requirements are

TABLE IV

HYPNOTIC POTENCY OF ACTIVE 2-PHENYLGLYCIDAMIDES IN THE MOUSE

Compd	HD_{50} ± SE, mg/kg ip	LD_{50} ± SE, mg/kg ip	Potency ratio LD_{50}/HD_{50}
54	48 ± 4	603 ± 58	13
45	101 ± 12	570 ± 56	5.6
56	126 ± 7	717 ± 86	5.7
57	85 ± 7	508 ± 46	6.0
63	120 ± 13	736 ± 74	6.1
65	85 ± 7	677 ± 73	8.0
67	65 ± 7	535 ± 62	8.2
69	85 ± 9	510	6.0
70	*a*	*a*	
74	300 ± 40	1300 ± 360	4.3
Glutethimide	90 ± 8	339 ± 33	3.8
Sodium pentobarbital	40 ± 2	126 ± 7	3.2

[a] At a single test dose of 180 mg/kg 4/10 animals exhibited a positive response. Insufficient sample prevented determination of lethality.

necessary for the production of hypnosis. With the exception of **70**, all the isomeric 2-phenylglycidamides possessing hypnotic activity at the standard test dose of 180 mg/kg ip are of the B configuration. The activity of **70**, one-half that of its B isomer **69**, remains an anomoly. Therefore, where isomeric pairs exist the following discussion will concern itself only with the B isomer.

The hypnotic potency of **54** is equal to that of sodium pentobarbital and twice that of glutethimide. Variations in the phenyl ring substituents in **54** have resulted in a decrease or loss of activity. Compound **69**, the 2-Me analog, possesses only one-half the activity of **54**, while analogs containing H at the 2 position of the phenyl ring and either H (**43**), Cl (**47**), Br (**49**), F (**51**), Me (**52**), or $MeSO_2$ (**53**) in the 4 position were inactive at 180 mg/kg ip. The 2,4-F_2 analog **71** also was inactive at this dose. These results imply the 2 substituent on the phenyl ring is important sterically for hypnotic activity, possibly by protecting the epoxide group from nucleophilic ring opening. Molecular models indicate the preferred conformation of the phenyl ring is such that the substituent at the 2 position of the phenyl ring lies below the C–C bond of the epoxide ring. In this conformation nucleophilic opening of the epoxide ring is sterically hindered by bulky substituents at the 2 position of the phenyl ring.

In constrast to the 2 substituent, the 4 substituent on the phenyl ring in **54** is not essential for activity, but the more active compounds contain a 4 substituent. Respectively, the 2,4-dichloro (**54**), 2-chloro-4-methyl (**67**), 2-chloro-4-fluoro (**65**), and 2-chloro (**45**) analogs possess HD_{50} values of 48, 65, 85, and 101. Substitution of Cl in the 5 position of the phenyl ring, **58**, **60**, and **61**, resulted in loss of hypnotic activity at the standard test dose of 180 mg/kg ip. In comparison, the 2,3,4-trichlorophenyl analog **63** had one-fourth the hypnotic potency of **54**.

Certain requirements for activity also exist for the substituents at the 3 position of the epoxide ring. The analogs containing H (**56**) or Br (**57**), instead of Cl on the epoxide ring were, respectively, one-fourth and one-half as active as **54**. Compound **73**, the 3-propyl analog, was inactive; however, the configuration of **73** is uncertain. Compound **74**, the analog having two Cl at the 3 position of the epoxide ring, had slightly less than one-fourth the activity of **54**.

All the compounds exhibited a wide margin of safety as indicated by the LD_{50} HD_{50} ratio. The onset of hypnosis induced by the active compounds was comparable to that of the reference hypnotics, although the duration of effect was less in most instances. Compound **54** had an especially high ratio and a duration that was comparable to the reference hypnotics. At 180 mg/kg ip **54** had a duration of 186 ± 10 min as compared to 147 ± 20 min for glutethimide (180 mg/kg ip) and 230 ± 30 min for sodium pentobarbital (100 mg/kg ip). Administered orally, the HD_{50} of **54** was 64 ± 6 mg/kg, while the LD_{50} was approximately 1000 mg/kg.

Compound **54** was hypnotic in the rabbit, cat, and dog at the intraperitoneal doses of 20 and 30 mg/kg with no evidence of respiratory depression; however, at 10 mg/kg in the rabbit no hypnosis was produced. A delayed onset attended by excitement was found in the cat at 20 mg/kg ip. In the dog a delayed onset without excitement occurred at doses of 32 mg/kg ip and 56 mg/kg *po*. Emesis preceeding hypnosis, tremors on awakening, and a long-lasting ataxia (48 hr) followed these doses in the dog. Other pharmacologic effects of **54** in the mouse included a suppression of pernicious preening behavior,[12] strychnine lethality,[13] and maximal electroshock seizures.[14] These effects occurred only at or near hypnotic dose levels.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Structure determinations were based essentially on microanalyses and comparison of ir and nmr spectral features within the given classes of compounds. Since no unusual spectral features were observed for these compounds, no absorption peaks are listed in the Experimental Section. Where analyses are represented only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

[10] W. R. Thompson, *Bacteriol. Rev.*, **11**, 115 (1947).

[11] J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Therap.*, **96**, 99 (1949).

[12] J. C. Wilson, J. F. Pods, and A. Kaldel, *Fed. Proc.*, **19**, 21 (1960).

[13] T. L. Kerley, A. G. Richards, R. W. Begley, R. E. Abrey, and L. C. Weaver, *J. Pharmacol. Exp. Therap.*, **132**, 360 (1961).

[14] E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952).

The following are representative of the methods used to prepare the compounds discussed in this paper.

Halogenated Acetophenones.—The following known halogenated acetophenones, not commercially available, were prepared by literature methods:[5,15] 2,2,2',4'-tetrachloroacetophenone,[5] 2,2,4'-trichloroacetophenone,[5,16] 4'-bromo-2,2-dichloroacetophenone,[5] 2,2-dichloro-4'-fluoroacetophenone,[16] 2,2-dichloro-4'-methylacetophenone,[17] 2,2-dichloro-4'-methylsulfonylacetophenone,[18,19] 2,2,2',5'-tetrachloroacetophenone,[5,20] 2,2,2',4',5'-pentachloroacetophenone,[15] 2,2',5'-trichloroacetophenone,[5,20] and 2,2,2',3',4'-pentachloroacetophenone.[21] 2,2-Dichloroacetophenone and 2,2-dichloro-3'-nitroacetophenone were purchased from Frinton Laboratories and Matheson Coleman and Bell Co., respectively.

2,2,2'-Trichloroacetophenone was prepared by the method of Falbe and Schulze-Steinen.[5] Cl_2 was bubbled into a stirred solution of 68 g (0.44 mole) of 2'-chloroacetophenone in 240 ml of glacial HCO_2H at 30° containing a small amount of HCl gas. The reaction temperature slowly rose to 50°. After 4 hr no starting material was detectable by glpc. After standing overnight the reaction mixture was poured into H_2O and the product was extracted with CH_2Cl_2. The extracts were washed with 5% $NaHCO_3$ solution and with H_2O and dried ($MgSO_4$). Solvent removal afforded 96 g (98%) of slightly yellow liquid. *Anal.* ($C_8H_5Cl_3O$) Cl.

2,2-Dibromo-2',4'-dichloroacetophenone was prepared by a slight modification of the previous procedure.[5] To a stirred solution of 78.5 g (0.415 mole) of 2',4'-dichloroacetophenone in 500 ml of glacial HCO_2H at 40° was added a few drops of Br_2. The solution was warmed slowly to 68° at which time the Br_2 color disappeared. At 68° the remainder of 133 g (0.83 mole, 43 ml) of Br_2 was added dropwise. After the addition was complete, two layers separated from the cooled reaction mixture. The lower layer was separated and the upper layer was poured into H_2O and extracted with CH_2Cl_2. The combined extracts and lower layer were washed (H_2O, 5% $NaHCO_3$ solution, H_2O) and dried ($MgSO_4$). Solvent removal afforded 142 g (98%) of slightly yellow liquid. *Anal.* ($C_8H_4Br_2Cl_2O$) Br, Cl, halogen equiv.

4'-Methoxy-2,2,3'-trichloroacetophenone was prepared in 84% yield, mp 90–92°, by the previously described procedure[5] utilizing 3 moles of Cl_2/mole of 4'-methoxyacetophenone. *Anal.* ($C_9H_7Cl_3O_2$) Cl.

2,2-Dichloro-2',4'-difluoroacetophenone was prepared in 85% yield, bp 79–84° (0.5–0.8 mm), by the procedure of Whetstone, *et al.*,[15] from *m*-difluorobenzene and dichloroacetyl chloride. *Anal.* ($C_8H_4Cl_2F_2O$) Cl.

4'-Fluoro-2,2,2'-trichloroacetophenone was prepared[15] from *m*-chlorofluorobenzene and dichloroacetyl chloride. Distillation of the crude product afforded a mixture of isomers, bp 134–136° (9.8–10.2 mm), from which the product was isolated in a 10% yield, mp 20° by repeated MeOH recrystallization. *Anal.* ($C_8H_4Cl_3FO$) C, H, Cl.

2'-Methyl-2,2,4'-trichloroacetophenone was prepared[15] from *m*-chlorotoluene and dichloroacetyl chloride. Vacuum distillation through a 20-plate bubble-cap column using a 20:1 reflux ratio afforded the product in 15% yield, bp 155–158° (11–12 mm), of 90% isomeric purity as evidenced by glpc. Due to the difficulty in separating the pure isomer, elemental analyses were not obtained. The ir spectrum was consistent with the assigned structure. This product was converted to the mandelamide (**39**, Table II), for which acceptable elemental analyses were obtained.

4'-Methyl-2,2,2'-trichloroacetophenone was obtained in a 15% yield of 95% isomeric purity (glpc) by hexane extraction of the pot residue from the distillation of 2'-methyl-2,2,4'-trichloroacetophenone. Elemental analyses were not obtained, but the ir spectrum was consistent with the assigned structure. This product was converted to the mandelamide (**38**, Table II), for which acceptable elemental analyses were obtained. The structure assignment of 2'-methyl-2,2,4'-trichloroacetophenone and 4'-methyl-2,2,2'-trichloroacetophenone was made on the basis of oxidation of the latter by alkaline $KMnO_4$[22] to the known 2-chloroterphthalic acid, mp 305° from H_2O (lit.[23] 316–318°).

2,2,2,2',4'-Pentachloroacetophenone.[5]—Cl_2 was added slowly over 30 hr with stirring to 307 g (1.19 moles) of 2,2,2',4'-tetrachloroacetophenone undergoing uv irradiation. The reaction temperature was maintained at 155–160°. The product was stripped under high vacuum to give 347 g (100%) of yellow liquid of 95% purity as indicated by glpc and ir. *Anal.* ($C_8H_3Cl_5O$) Cl: calcd, 60.7; found, 61.2.

2,4-Dichloro-α-(dichloromethyl)mandelonitrile (8).—To a stirred solution of 202 g (0.783 mole) of 2,2,2',4'-tetrachloroacetophenone in 80 ml (2.0 moles) of HCN at 15° was added 15 drops of freshly prepared saturated aqueous KCN solution. A vigorous exothermic reaction occurred causing refluxing of the HCN. After 15 min of refluxing, 100 ml of Et_2O was added and the excess HCN was removed by distillation into a NaOH solution. Recrystallization of the resultant product from hexane–benzene (95:5) gave 187 g (84%) of colorless product, mp 93–95°. *Anal.* ($C_9H_5Cl_4NO$) N, Cl.

2-Chloro-α-(dichloromethyl)-4-fluoromandelonitrile (16).—To a vigorously stirred, heterogeneous mixture of 40.0 g (0.165 mole) of 2,2,2'-trichloro-4'-fluoroacetophenone and 21 g (0.43 mole) of NaCN in 35 ml of Et_2O and 55 ml of H_2O at 5–7° was added over 15 min 33.3 ml (0.40 mole) of concentrated HCl. After 30 min at 3° the vigorously stirred solution was allowed to warm slowly to 23° over a period of 1.5 hr. Concentrated HCl (10 ml) was added, the Et_2O layer separated, and the aqueous layer was extracted with Et_2O. The combined Et_2O fractions were dried ($MgSO_4$). Filtration, solvent removal, and recrystallization from Et_2O gave 36.9 g (83%) of colorless product, mp 96–98°.

2,4-Dichloro-α-(dichloromethyl)mandelamide (29).—A stirred suspension of 300 g (1.05 moles) of **8** in 1 l. of 80% H_2SO_4 was heated on a steam bath for 16 hr, cooled, and poured over ice. The resultant gummy solid was dissolved in CH_2Cl_2, dried ($MgSO_4$), and cooled to afford 258 g (81%) of **29**, mp 135–137°.

α-(Chloromethyl)-2,5-dichloromandelamide (34).—A suspension of 25.0 g (0.10 mole) of α-(chloromethyl)-2,5-dichloromandelonitrile in 125 ml of 90% H_2SO_4 was stirred at room temperature for 16 hr and poured over ice, and the resultant white crystals were filtered to afford 26 g (97%) of **34**, mp 151.5–156°.

3-Chloro-2-(2,4-dichlorophenyl)glycidamide (54 and 55). Method A.—To a stirred suspension of 2.4 g (0.05 mole of NaH) of hexane-washed 50% NaH–mineral oil suspension in 50 ml of anhydrous THF was added all at once a solution of 15 g (0.05 mole) of **29** in 100 ml of anhydrous THF. An exothermic reaction occurred with H_2 evolution and the formation of a white precipitate. The reaction mixture was stirred for 6 hr, poured into H_2O, and extracted with Et_2O. The Et_2O extracts were washed with H_2O and dried ($MgSO_4$) and the solvent was removed to afford a yellow, viscous liquid. Recrystallization from CH_2Cl_2–C_6H_{14} gave 6 g of white crystals, mp 115–121°, containing 85% of **54** and 15% of **55** by nmr analysis. Elution chromatography through silica gel G using Et_2O as the eluent afforded 600 mg of crude **55** and 4.2 g of crude **54**. Recrystallization from CH_2Cl_2–C_6H_{14} gave 400 mg (5%) of **55**, mp 170–171.5°, and 3.1 g (23%) of **54**, mp 122–123°.

Method B.—To a stirred solution of 60.6 g (0.20 mole) of **29** in 175 ml of anhydrous MeOH was added dropwise a solution of 10.8 g (0.20 mole) of NaOMe in 100 ml of anhydrous MeOH. The resulting solution was stirred at room temperature for 6 hr and allowed to stand overnight. The reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O and dried ($MgSO_4$), and the solvent was removed to afford a crude mixture of **54** and **55**. Elution chromatography through silica gel G using Et_2O as the eluent gave, after recrystallization from CH_2Cl_2–C_6H_{14}, 34.3 g (64%) of **54**, mp 122–124°, and 1.7 g (3%) of **55**, mp 169.5–170°.

2-(2,4-Dichlorophenyl)-2-hexenenitrile (VI).—To a stirred mixture of 37.2 g (0.20 mole) of 2,4-dichlorobenzyl cyanide and 29 g (0.40 mole) of butyraldehyde was added with cooling a

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methanolic KOH solution prepared from 0.1 g of KOH and 50 ml of MeOH. The reaction was heated to 60° for 1 hr, during which an additional 36 g (0.50 mole) of butyraldehyde was added since glpc indicated the butyraldehyde was undergoing self-condensation to 2-ethyl-2-hexenal. The mixture stood at room temperature for 2.5 days. Addition of 85% H_3PO_4 until acidic, stripping of the solvent, and vacuum distillation afforded 17 g (35%) of liquid VI, bp 125–128° (0.05 mm). *Anal.* ($C_{12}H_{11}Cl_2N$) N; Cl: calcd, 29.6; found, 28.5.

2-(2,4-Dichlorophenyl)-3-propylglycidamide (73).—A stirred mixture of 6.0 g (0.025 mole) of VI, 5 ml of 30% H_2O_2, 10 ml of Na_2CO_3 solution, and 30 ml of AcMe was heated at 52° for 30 min. Cooling, filtration of the resultant white crystals, and recrystallization from EtOH gave 3.5 g of **73**, mp 161–162°. The original filtrate afforded an additional 2.5 g of **73**, mp 160–161°, from C_8H_{14}–C_6H_6. The total yield was 6.0 g (88%).

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Analgetics. II. Relationship between Structure and Activity of Some β-Amino Ketones[1,2]

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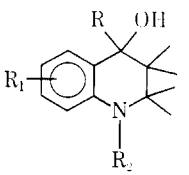
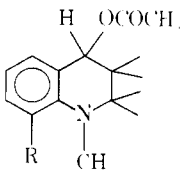
A number of substituted 1,2,3,4-tetrahydro-4-quinolinols and related compounds were prepared and found devoid of analgetic activity. The successful synthesis of a series of β-aminopropiophenones, considered to be open-chain analogs of active 2,3-dihydro-4-quinolones, yielded compounds more potent than their closed-ring analogs.

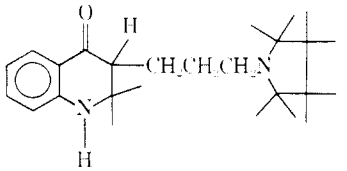
The reported analgetic activity of several 2,3-dihydro-4-quinolones[3] suggested the synthesis and biological examination of a number of analogous compounds. Those studied include a series of 1,2,3,4-tetrahydro-4-quinolinols (I), esters of two of these alcohols (II), a 2,3-dihydro-4-quinolone substituted at C-3 by an ω-N-pyrrolidinopropyl group (III), a series of β-aminopropiophenones (IV), and three 1-alkyloctahydro-4-quinolones (V).



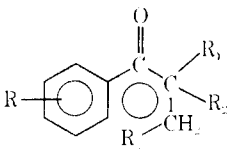
I, R = H, C_6H_5, $C_6H_5CH_2$, *n*-C_4H_9
R_1 = H, OCH_3
R_2 = H, alkyl, alkenyl or acyl



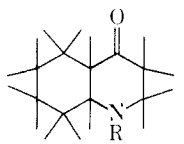
II, R = H or OCH_3



III



IV, R = H, OCH_3, or OH
R_1 and R_2 = H or CH_3
R_3 = alkylamino or dialkylamino



V, R = CH_3, C_2H_5, *n*-C_3H_7

The 1,2,3,4-tetrahydro-4-quinolinols (Table I) were prepared from the corresponding ketone by $NaBH_4$ reduction (method A) or by the addition of a Grignard reagent (method B). While we were unable to esterify the tertiary alcohols, two of the secondary alcohols were converted successfully by CH_2CO to the corresponding acetates. A 2,3-dihydro-4-quinolone having a pyrrolidinopropyl group in the 3 position was prepared by aluminum isopropoxide oxidation of the previously reported[3] 3-[3-(N-pyrrolidinopropyl)]-1,2,3,4-tetrahydro-4-quinolinol.

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(2) Portions of this report were abstracted from the Ph.D. dissertations of M. S. Atwal and M. Megahy, and the M.S. dissertation of C. Pokorny.

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