fate, stripped and the residue distilled *in vacuo*. There was obtained 255 g. (88% yield) of the hydroxyamine, b. p. 178° (1 mm.).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.2; H, 8.4. Found: C, 76.1; H, 8.6.

In Table II are analogs which were prepared in a similar manner. In cases where the alkylaminoethanol hydrohalides were oils, the supernatant liquid was decanted and worked up as described above. In several cases, the hydrochlorides of the products were so water insoluble that three layers formed on extraction with dilute hydrochloric acid. If this happened, the two lower layers were drawn off together as the acid extract.

β-Chloroethylamine Hydrochlorides (XI)

Method A.—To an ice-cold, well-stirred solution of 0.1 mole of the β-hydroxyethylamine (X) in 100 ml. of chloroform was added dropwise 15 ml. of thionyl chloride. After the addition was complete, the mixture was allowed to come to room temperature and finally refluxed for one hour. The solvent and excess thionyl chloride were evaporated under reduced pressure. The residual oil was taken up in 50 ml. of benzene and the solvent again evaporated under reduced pressure. This treatment with benzene was repeated and the residue then crystallized from a suitable solvent.

Method B.—A solution of 0.1 mole of the β-hydroxyethylamine in 100 ml. of ether was added dropwise to an ice-cold, stirred solution of 15 ml. of thionyl chloride in 100 ml. of ether. After the addition was complete, the mixture was refluxed one to three hours. In most cases, the product had solidified at this point, so it was collected by filtration and recrystallized. If the product remained an oil, it was worked up as described under method A.

Method C.—This method differed from method B only in the order of addition; thionyl chloride was added to the solution of the β-hydroxyethylamine.

The data on the β-chloroethylamine hydrochlorides are contained in Table III.

Pharmacology.—A detailed report on the pharmacology of these compounds will be published by S. Loewe and L. S. Goodman. The most active compounds are those in which R, R′ and R‴ represent hydrogen and R″ is ethyl or isopropyl. These compounds are about five times as active as "Dibenamine" as sympatholytics and more active than "Benadryl" as antihistaminics.

Acknowledgment.—The authors are indebted to Mr. Richard M. Downing and Mrs. Neva Knight who performed the microanalyses reported herein.

Summary

A series of N-β-(benzylphenoxy)-ethyl-N-β-chloroethylalkylamine hydrochlorides has been prepared. Certain members of this series display sympatholytic activity or antihistaminic activity in animals.

SYRACUSE, NEW YORK RECEIVED AUGUST 25, 1949

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Halogen Containing Ketones, Esters and Carbinols Related to Methadone

BY M. E. SPEETER, L. C. CHENEY AND S. B. BINKLEY

The acylation of carbinols derived from the synthetic analgesics methadone, isomethadone and related ketones has been reported earlier from these laboratories.[1] Studies of other workers with some of these derivatives have appeared[2,3] and the properties of some of the optically active forms given.[4] This paper reports the high analgesic potency of some halogen containing esters of carbinols derived from methadone and related ketones.

The potentiating effect of halogen substitution when present in the acyl group made it of interest to determine the effect of halogen substitution in the phenyl ring. The increase in activity afforded by halogen substitution in the antimalarials[5,6] and the antihistaminics[7] has been established. In the O.P.B. 981[8] it is stated that for maximum activity the two phenyl groups in compounds of the methadone series must not be sub-

TABLE I

HALOGEN CONTAINING ESTERS $(C_6H_5)_2C(R_1)(OR_2)CH(CH_3)CH_2$

R_1	R_2	M. p., °C., uncor.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Yield, %	LD_{50}[a]	Analgesia[b]	Activity index[c]
CH_2-$CH(CH_3)N(CH_3)_2$	$ClCH_2CO$-[d]	195–196	$C_{23}H_{30}ClNO_2 \cdot HCl$	65.08	64.80	7.36	7.43	47	13.3 ± 2	0.75	18
CH_2-$CH(CH_3)N(CH_3)_2$	$BrCH_2CO$[e]	190–191	$C_{23}H_{30}BrNO_2 \cdot HBr$	53.80	53.60	6.08	6.25	73	23 ± 2	5.0	4.0
$CH(CH_3)$-$CH_2N(CH_3)_2$	$ClCH_2CO$-[d]	205–206	$C_{23}H_{30}ClNO_2 \cdot HCl$	65.08	65.05	7.36	7.37	39	ca. 70	8.0	8.7
$-CH(CH_3)-CH_2N(CH_3)_2$	$ClCH_2CH_2OCO$-[d]	188–189	$C_{24}H_{32}ClNO_3 \cdot HCl$	63.43	63.40	7.32	7.28	62	220 ± 10	25	9.0
$-CH_2-CH_2-NC_4H_8O$[f]	$ClCH_2CO$-[e]	229–231	$C_{24}H_{30}NO_3 \cdot HCl$	63.71	63.70	6.91	6.97	65	105 ± 15	3	35
$-CH_2-CH(CH_3)NC_4H_8O$	$ClCH_2CO$-[g]	195–196	$C_{25}H_{32}ClNO_3 \cdot HCl$	64.36	63.90	7.13	7.28	..	77 ± 11	1	77

[a] Intraperitoneal LD_{50} in the mouse in mg./kg. [b] Subcutaneous minimal analgesic dose in guinea pig in mg./kg. [c] For comparison the activity index (LD_{50} ÷ effective dose) for methadone measured by the same pharmacological methods is 2.3. [d] Recryst. from isopropyl alcohol. [e] Recryst. from ethanol. [f] $-NC_4H_8O$ represents morpholinyl. [g] Recryst. from methyl isobutyl ketone; yield not recorded.

These esters, shown in Table I, were prepared by the procedures developed earlier.[1]

(1) Speeter, Byrd, Cheney and Binkley, THIS JOURNAL, **71**, 57 (1949).

(2) May and Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(3) May and Mosettig, *ibid.*, **13**, 663 (1948).

(4) Pohland, Marshall and Carney, THIS JOURNAL, **71**, 460 (1949).

(5) Board for Coördination of Malarial Studies, *Science*, **103**, 8 (1946).

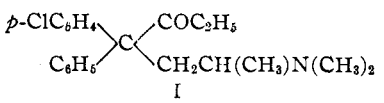
(6) Gurd, *Nature*, **158**, 707 (1946).

(7) Tislow, LaBelle, Makovsky, Reed, Cunningham, Emele, Grandage and Roggenhofer, *Federation Proc.*, **8**, 338 (1949).

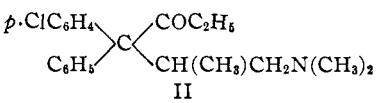
(8) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of the Publication Board, Department of Commerce, Washington, D. C., p. 93.

stituted in any way. From the tabulated compounds of O.P.B. 981 it appeared that this rule was established on the basis of hydroxy and methoxy substituents alone. Since the studies reported here were completed Bockmühl and Ehrhart[9] have described 4,4-di-*p*-chlorophenyl-6-dimethylamino-3-hexanone and Weiss, Cordasco and Reiner[10] have reported the *p,p'*-dichloro derivative of methadone. Both compounds are inactive as analgesics.

The mono-*p*-chloro derivatives of methadone (I) and isomethadone (II) prepared in these laboratories were assigned the structures given through consideration of the similarities of the isolation procedures for these compounds to the isolation procedures used for the unsubstituted ketones. The ketone (I) was quite readily isolated from the reaction mixture as a highly insoluble hydrobromide salt. The mother liquors



I



II

failed to give crystalline material through any of the usual procedures so the heavy oil isolated was converted to the base. Previous studies[11,12,13] have shown that isomethadone remains as a stable imine in the methadone synthesis, and that methadone imine can be isolated only if very mild hydrolytic conditions are used. Proceeding on the assumption that a very high percentage of any imine present in an ether solution of the basic mixture would have the "iso" structure, excess acetyl chloride was added to a cooled ether solution of the material and the precipitated acetylimine corresponding to (II) collected. After prolonged acid hydrolysis of the mixture two products were isolated as hydrochlorides; one melting at 206–208° analyzed correctly for the ketone (II), the other, m. p. 268–269°, has not been identified.

The activity indices of the chloroacetyl esters are all somewhat greater than the corresponding unsubstituted esters. In contrast to the potentiating effect of halogen in the acyl group is the complete lack of analgesic potency in the *p*-chloro substituted ketone (I). Reduction of (I) to the carbinol and acetylation gave a compound of very low analgesic activity.

Acknowledgments.—We wish to express our appreciation to Mr. R. M. Downing for the microanalyses recorded herein. We also wish to thank Dr. Carl C. Pfeiffer of the University of Illinois Medical School for permission to present the pharmacological data.

(9) Bockmühl and Ehrhart, *Ann.*, **561**, 52–85 (1948).
(10) Weiss, Cordasco and Reiner, THIS JOURNAL, **71**, 2650 (1949).
(11) Cheney, Smith and Binkley, *ibid.*, **71**, 53 (1949).
(12) Schultz, Robb and Sprague, *ibid.*, **69**, 188, 2454 (1947).
(13) Easton, Gardner, Evanick and Stevens, *ibid.*, **70**, 76 (1948).

Experimental

α-*p*-Chlorophenyl-α-phenylacetonitrile.—This compound was prepared according to the procedure of Schultz, Robb and Sprague[12] for diphenylacetonitrile with the substitution of *p*-chlorophenylacetonitrile[14] for phenylacetonitrile. The crude nitrile distilled at 170–175° at 1 mm. The distillate solidified and melted at 75–76° after recrystallization from isopropyl alcohol; yield, 116 g. (52%). *Anal.* Calcd. for $C_{14}H_{10}ClN$: C, 74.0; H, 4.46. Found: C, 74.3; H, 4.48.

4-Dimethylamino-2-*p*-chlorophenyl-2-phenylvaleronitrile and 4-Dimethylamino-3-methyl-2-*p*-chlorophenyl-2-phenylbutyronitrile.—α-*p*-Chlorophenyl-α-phenylacetonitrile was condensed with 1-dimethylamino-2-chloropropane using lithium amide. The heavy oil of mixed isomeric ketones obtained in a yield of 89% was used directly in the next step.

4-*p*-Chlorophenyl-6-dimethylamino-4-phenyl-3-heptanone and 4-*p*-Chlorophenyl-6-dimethylamino-5-methyl-4-phenyl-3-hexanone.—A solution of ethylmagnesium bromide was prepared in 300 ml. of ether from 109.9 g. (1.0 mole) of ethyl bromide and 28 g. (1.15 g. atoms) of magnesium. To the Grignard reagent was added 110 g. (0.35 mole) of the mixed nitriles, obtained in the above reaction, in solution in 200 ml. of xylene. The mixture was refluxed for six hours and was poured while still warm into a mixture of 800 ml. of water and 400 ml. of concentrated hydrochloric acid. When the vigorous reaction had subsided and the mixture had cooled somewhat, 200 ml. of benzene was added. Three layers soon separated and the heavy, red middle layer gradually crystallized when the mixture was cooled. The solid was filtered after three days and a large amount of red oil pressed from the solid. It was recrystallized from water; m. p. 128–140° with loss of solvent. The oil resolidified to melt at 188–191°. The product was in turn recrystallized from methyl isobutyl ketone and twice from chloroform–ethyl acetate; m. p. 193–194.5°. *Anal.* Calcd. for $C_{21}H_{26}ClNO\cdot HBr$: C, 59.34; H, 6.40. Found: C, 59.80; H, 6.34.

The addition of sodium hydroxide to a solution of the hydrobromide in water gave an oil which solidified on scratching. After recrystallization from ethanol the crystals melted at 83–84°. *Anal.* Calcd. for $C_{21}H_{26}ClNO$: C, 73.32; H, 7.63. Found: C, 73.20; H, 7.59.

For pharmacological testing the hydrochloride salt was prepared by passing dry hydrogen chloride into an ether solution of the above base. The 4-*p*-chlorophenyl-6-dimethylamino-4-phenyl-3-heptanone hydrochloride which separated was recrystallized from methyl isobutyl ketone; m. p. 198–199°. *Anal.* Calcd. for $C_{21}H_{26}ClNO\cdot HCl$: C, 66.31; H, 7.10. Found: C, 66.20; H, 7.08.

The water layer from the hydrolysis of the Grignard reaction was investigated for the "iso" product in solution as the soluble imine hydrochloride. The solution was neutralized and a heavy oil liberated. The oil was extracted into ether and a portion concentrated. All attempts to obtain a crystalline base or salts from the oil were unsuccessful. The ether solution was diluted to a volume of two liters and acetyl chloride added to the cooled solution until no further reaction or precipitation was evident. The twenty-five grams of white precipitate obtained recrystallized poorly from all solvents. The solid was refluxed forty-eight hours with 250 ml. of concentrated hydrochloric acid. The mixture was made basic, extracted into ether, dried and the ether solution saturated with dry hydrogen chloride. The gummy precipitate was extracted with hot methyl isobutyl ketone which deposited crystals on cooling; m. p. 200–203°. The solid was recrystallized from methyl isobutyl ketone; m. p. 206–208°. This material when mixed with the hydrochloride of (I) melted below 180°. *Anal.* Calcd. for $C_{21}H_{26}ClNO\cdot HCl$: C, 66.31; H, 7.10; N, 3.68. Found: C, 65.90; H, 7.03; N, 4.14.

The solid remaining after the extraction with methyl isobutyl ketone was dissolved in ethanol and white crystals separated on cooling. After three recrystallizations from

(14) Walther and Wetzlich, *J. prakt. Chem.*, [2] **61**, 187 (1900).

ethanol the material melted at 268–269°. The analytical data obtained does not fit any expected by-product. Found: C, 58.7; H, 7.12; N, 6.14.

6-Dimethylamino-4-*p*-chlorophenyl-4-phenyl-3-heptanol.—Seventeen grams (0.04 mole) of (I) as the hydrobromide salt was converted to the base with alkali, taken into ether and the solution dried carefully. The solution was added to an ether solution of 2 g. (0.05 mole) of lithium aluminum hydride in 500 ml. of ether. The mixture was refluxed sixteen hours and cooled in an ice-bath. The excess lithium aluminum hydride was destroyed through the cautious addition of 200 ml. of 10% sodium hydroxide dropwise to the stirred reaction mixture. The ether layer was separated and the water layer extracted with 500 ml. of ether. The combined ether solutions were dried over potassium carbonate and concentrated. The residual oil solidified and was recrystallized from ligroin (b. p. 60–71°). The yield was 13.6 g. of product melting at 136–138°. *Anal.* Calcd. for $C_{21}H_{28}ClNO$: C, 72.89; H, 8.17. Found: C, 73.00; H, 8.05.

3-Acetoxy-6-dimethylamino-4-*p*-chlorophenyl-4-phenylheptane Hydrochloride.—Three grams of the 6-dimethylamino-4-*p*-chlorophenyl-4-phenyl-3-heptanol was dissolved in 50 ml. of ethyl acetate and refluxed with 2 ml. of acetyl chloride for one hour. The solution was cooled and the solid which separated filtered and recrystallized from ethyl acetate. After three recrystallizations, 2.5 g. of crystals melting at 230–231° was obtained. *Anal.* Calcd. for $C_{23}H_{30}ClNO_2 \cdot HCl$: C, 65.08; H, 7.36. Found: C, 65.03; H, 7.37.

2-Chloroethyl 6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexyl-carbonate Hydrochloride.—A mixture of 5 g. (0.0161 mole) of 6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanol, 3 g. (0.021 mole) of 2-chloroethyl chloroformate and 50 ml. of ethyl acetate was boiled under reflux for one hour and then cooled. The salt which separated was collected by filtration and recrystallized twice from isopropyl alcohol to obtain 4.5 g. of colorless crystals, m. p. 188–189°; *cf.* Table I.

Summary

The preparation of some halogen containing esters related to methadone is reported. The synthesis of methadone and isomethadone with a chlorine substituent on one benzene ring is presented.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XXI. The Dealcoholation of Orthoesters. Dimethylketene Dimethylacetal

BY S. M. MCELVAIN AND JAMES T. VENERABLE[1]

Of all the methods now available for the preparation of ketene acetals, the direct dealcoholation of an orthoester would appear to be the most promising from the standpoint of general applicability. However, this method has had quite limited success. Such an orthoester as I, in which R is the negative cyano or carbethoxy group, may be pyrolyzed smoothly in the presence of a trace of acid catalyst to the corresponding ketene acetal (II),[2] but when the less negative phenyl group is the α-substituent, a considerable amount (20–33%) of the normal ester is formed concurrently with the ketene acetal.[3] The normal ester appears to be formed, when R is phenyl and R′ is ethyl, by the loss of ethylene from the ketene acetal (II) at the temperature of pyrolysis; in the case of the methyl orthophenylacetate a complex sequence of reactions has been postulated to account for its pyrolysis to methyl phenylacetate.[3] The pyrolysis of such an orthoester as ethyl orthoacetate yields only the normal ester as the initially formed ketene acetal is further pyrolyzed to ethyl acetate and ethylene at the higher temperature required for the dealcoholation of the orthoester.[4]

$$\underset{\text{I}}{RCH_2C(OR')_3} \longrightarrow \underset{\text{II}}{RCH{=}C(OR')_2} + R'OH$$

The preparation of tetraethoxyethylene (V) from pentaethoxyethane (III) involved a novel method of dealcoholation of an orthoester, *viz.*, the removal of the elements of alcohol at ordinary temperatures by means of a strong base,[5] sodium ethyl. This dealcoholation was thought to involve an acid–base reaction in which the ethyl anion removed the single proton from the α-carbon of the orthoester (III) to form the anion (IV) which then passed into the ketene acetal (V) by the expulsion of an ethoxyl anion. However, other reactions were involved in the action of sodium ethyl on III; the yield of V was only 39% while the yields of ethane and sodium ethoxide were 160 and 235%, respectively, on the basis of the reaction

$$\underset{\text{III}}{(C_2H_5O)_2CHC(OC_2H_5)_3} + \overset{+}{Na}\overset{-}{C_2H_5} \longrightarrow$$

$$C_2H_6 + \underset{\text{IV}}{(C_2H_5O)_2\overset{-}{C}{-}C(OC_2H_5)_3Na^+} \longrightarrow$$

$$\underset{\text{V}}{(C_2H_5O)_2C{=}C(OC_2H_5)_2} + NaOC_2H_5$$

It is apparent that the sodium ethyl removed hydrogens from the ethoxyl groups, as well as the single one on the α-carbon of the orthoester III, to produce the amount of ethane that is formed in this reaction; also the high yield of sodium ethoxide indicates still another mode of reaction. Nevertheless, this reasonably successful low temperature dealcoholation of III in-

(1) Wisconsin Alumni Research Foundation Research Assistant, 1946–1949.

(2) McElvain and Schroeder, THIS JOURNAL, **71**, 47 (1949).

(3) McElvain and Stevens, *ibid.*, **68**, 1917 (1946).

(4) McElvain, Anthes and Shapiro, *ibid.*, **64**, 2525 (1942).

(5) McElvain and Clarke, *ibid.*, **69**, 2661 (1947).