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Chloro Analogs of Methadone

BY PHILIP WEISS, M. G. CORDASCO AND L. REINER

Since the first report[1] on the analgesic 6-dimethylamino - 4,4 - diphenylheptanone - 3, also known as no. 10820, Amidone, and methadone, several analogs of this compound have been prepared in an attempt to find an analgesic having increased potency.[2,3,4] Most of these were less active than the parent compound with the exception of May and Mosettig's 3-acetoxy-6-dimethylamino-4,4-diphenylheptane hydrochloride[3] whose activity compares favorably with that of methadone. They also prepared the 3-chloro-6-dimethylamino-4,4-diphenylheptane which was almost inactive.

Although the original German investigators found that nuclear substitutions in methadone decrease its effectiveness, no specific reference was made to nuclear halogenation. This appeared to be of interest to us not only because the pharmacologic activity of some anti-infectives[5,6,7] show increased activity over that of the parent compound when the aromatic nuclei in them are chlorinated, but also because a simple method for the preparation of 6-dimethylamino-4,4-bis-(*p*-chlorophenyl)-heptanone-3 appeared to be possible starting from "D.D.T." The 6-dimethylamino-4-(*p*-chlorophenyl) - 4 - (*p* - chlorobenzyl)-heptanone-3 was also prepared. The reactions used in synthesizing these compounds are presented in the scheme.

Crude "D.D.T." was recrystallized from ethanol and the pure 1,1-bis-(*p*-chlorophenyl)-2,-2,2-trichloroethane (I) was converted to 1,1-bis-(*p*-chlorophenyl)-acetic acid (II) following the procedure of Grummitt, *et al.*,[8] by refluxing I with potassium hydroxide in diethylene glycol. The 1,1-bis-(*p*-chlorophenyl)-acetyl chloride (III), obtained by refluxing the acid with thionyl chloride in dry benzene, reacted with anhydrous ammonia, yielding 1,1-bis-(*p*-chlorophenyl)-acetamide (IV). Dehydration of the amide with acetic anhydride produced the desired 1,1-bis-(*p*-chlorophenyl)-acetonitrile (V). Saponification of the nitrile to II was effected by refluxing with alcoholic potassium hydroxide. Refluxing V with sulfuric acid yielded IV.

2,3-bis-(*p*-Chlorophenyl)-propionitrile (IX) was obtained by condensing *p*-chlorobenzyl cyanide with *p*-chlorobenzyl chloride using sodamide. This compound yielded 1,2-bis-(*p*-chlorophenyl)-propionic acid (X) upon saponification.

The nitriles (V and IX), treated with 1-dimethylamino-2-chloropropane in the presence of sodamide,[1] yielded oily products which were not further purified. Based on the results obtained by Schultz, *et al.*,[9,10] it may be assumed that the products contained both the 2,2-bis-(*p*-chlorophenyl)-4-dimethylaminopentane nitrile (VI) and 2 - (*p* - chlorophenyl) - 2 - (*p*-chlorobenzyl) - 4-dimethylaminopentane nitrile (XI) and their respective 3-methylbutane isomers. The 1-dimethylamino-2-chloropropane was prepared by the reaction of 1-chloropropanol-2 with aqueous dimethylamine and refluxing the resulting 1-dimethylaminopropanol-2 with thionyl chloride in dry benzene. Conversion of the amino nitriles (VI, XI) to the respective amino ketones (VII, XII) was effected by reaction with ethylmagnesium bromide. The ketimines were readily hydrolyzed to the ketones which is known to be characteristic of the Amidone type of structure in contrast to that of iso-Amidone.[9,11,12] It is therefore concluded that the isolated hydrochlorides were those of 6-dimethylamino-4,4-bis-(*p*-chlorophenyl)-heptanone-3 (VII) and the 6 - dimethylamino - 4 - (*p* - chlorophenyl) - 4-(*p*-chlorobenzyl)-heptanone-3 (XII).

Neither of these two chloro substituted analogs of methadone showed appreciable activity when tested on mice. The compounds did not produce a Straub phenomenon in doses up to one-half of the 50% lethal dose ($L.D._{50}$). The $L.D._{50}$ of both was about the same for mice, *i. e.*, 60 mg./kg.

Experimental[13]

1,1-bis-(*p*-Chlorophenyl)-acetic Acid (II).—Following the procedure of Grummitt and co-workers,[8] 114 g. of recrystallized 1,1-bis-(*p*-chlorophenyl)-2,2,2-trichloroethane,[14] 1200 ml. of diethylene glycol and 189 g. of potassium hydroxide when refluxed for six hours at 135° yielded 72 g. (83%) of the desired acid (II); m. p. 166°.

(1) Office of the Publication Board, Department of Commerce, Report No. PB-981, pp. 85–98.

(2) F. F. Blicke and A. J. Zambito, Abstracts of Papers of the American Chemical Society meeting, p. 3K (April, 1947).

(3) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(4) F. F. Blicke and J. Krapcho, Abstracts of Papers of the American Chemical Society meeting, p. 3K (April, 1948).

(5) (a) E. Klarman, U. S. Patent 2,010,598 (1935); U. S. Patent 2,139,550 (1938); (b) L. E. Mills, U. S. Patent 2,087,986 (1937); U. S. Patent 2,176,010 (1939).

(6) (a) J. S. Buck, L. Reiner and M. B. Sherwood, U. S. Patent 2,336,465 (1943); (b) A. S. Dubois and D. Dibblee, *Science*, **103**, 734 (1946); (c) C. A. Lawrence, C. E. Kwartler, V. L. Wilson and E. W. Kivela, *J. Am. Pharm. Assoc. Sc. Ed.*, **36**, 11 (1947).

(7) M. Rubin, H. C. Marks, H. Wishinsky and A. Lanzilotti, THIS JOURNAL, **68**, 623 (1946).

(8) O. Grummitt, A. Buck and R. Egan, *Org. Syntheses*, **26**, 21 (1946).

(9) E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

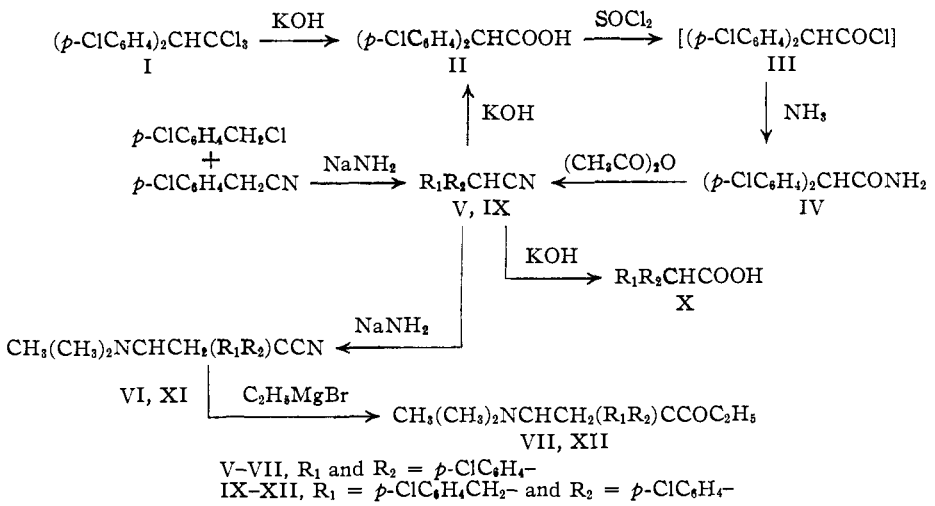
(10) E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948).

(11) N. R. Easton, J. H. Gardner, M. E. Evanick and J. R. Stevens, *ibid.*, **70**, 76 (1948).

(12) L. C. Cheney, R. R. Smith and S. B. Binkley, *ibid.*, **71**, 53 (1949).

(13) All melting points and boiling points given are uncorrected.

(14) Commercial grade "D. D. T." purchased from J. T. Baker and Co. was recrystallized from ethanol; m. p. 108–109°.



V–VII, R_1 and R_2 = p-ClC_6H_4–
IX–XII, R_1 = p-$ClC_6H_4CH_2$– and R_2 = p-ClC_6H_4–

1,1-bis-(p-Chlorophenyl)-acetyl Chloride (III).—A solution containing 90 g. (0.3 mole) of 1,1-bis-(p-chlorophenyl)-acetic acid in 1 liter of dry benzene was placed in a three-necked two-liter flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. To the cold solution was added dropwise 119 g. (1 mole) of thionyl chloride, and was refluxed for five hours. The excess thionyl chloride and benzene were removed *in vacuo*. The thionyl chloride was removed by repeated addition and removal of 200-ml. portions of dry benzene. The residue, 1,1-bis-(p-chlorophenyl)-acetyl chloride, was dissolved in 200 ml. of dry benzene and used directly in the preparation of the amide (IV).

1,1-bis-(p-Chlorophenyl)-acetamide (IV).—Anhydrous ammonia was passed into the benzene solution of 1,1-bis-(p-chlorophenyl)-acetyl chloride until precipitation was completed. The reaction mixture was concentrated to 100 ml., cooled and the crude amide filtered; m. p. 157–157.5° after recrystallization from benzene; yield 55 g. (65%).

Anal. Calcd. for $C_{14}H_{11}Cl_2NO$: Cl, 25.35; N, 5.00. Found: Cl, 25.56; N, 4.95.

1,1-bis-(p-Chlorophenyl)-acetonitrile (V).—To 9 g. (0.32 mole) of 1,1-bis-(p-chlorophenyl)-acetamide was added 45 ml. of acetic anhydride and refluxed for four hours. The excess acetic anhydride was removed under reduced pressure. The residue was recrystallized from ether; yield 7.5 g. (89%); m. p. 91–92°.

Anal. Calcd. for $C_{14}H_9Cl_2N$: Cl, 27.09; N, 5.34. Found: Cl, 27.20; N, 5.40.

Saponification of the nitrile with alcoholic potassium hydroxide yielded the known 1,1-bis-(p-chlorophenyl)-acetic acid; mixed m. p. 166°. Hydrolysis of the 1,1-bis-(p-chlorophenyl)-acetonitrile with sulfuric acid yielded the previously described 1,1-bis-(p-chlorophenyl)-acetamide (IV); mixed m. p. 157°.

2,3-bis-(p-Chlorophenyl)-propionitrile (IX).—To 21.5 g. (0.5 mole) of sodamide there was added, dropwise, during the course of one hour, 75 g. (0.5 mole) of p-chlorobenzyl cyanide in 300 ml. of dry toluene. After heating the red colored reaction mixture at 50° for one hour, 80.5 g. (0.5 mole) of p-chlorobenzyl chloride was added dropwise; this required one-half hour. The mixture was heated on a water-bath for two hours, cooled, and cautiously poured into water. The water layer was extracted with ether, combined with the toluene layer, and dried over anhydrous potassium carbonate. The solvents were removed; the oily residue was distilled *in vacuo*, and the fraction distilling at 200–215° (2 mm.) was collected. The colorless oil solidified on cooling. Recrystallization from ethyl alcohol yielded 50.3 g. (36%); m. p. 91–92°.

Anal. Calcd. for $C_{15}H_{11}Cl_2N$: Cl, 25.45; N, 5.09. Found: Cl, 25.72; N, 4.96.

2,3-bis-(p-Chlorophenyl)-propionic Acid (X).—One and one-half grams of 2,3-bis-(p-chlorophenyl)-propionitrile was added to 25 ml. of a 50% alcoholic potassium hydroxide solution and refluxed for two hours. The mixture was acidified with dilute hydrochloric acid, and the alcohol was removed by distillation *in vacuo*. The aqueous solution was extracted with ether and the extract was dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was twice recrystallized from ethanol; m. p. 163–165°; yield 1.1 g. (69%).

Anal. Calcd. for $C_{15}H_{12}Cl_2O_2$: Cl, 24.06. Found: Cl, 23.89.

2,2-bis-(p-Chlorophenyl)-4-dimethylaminopentane Nitrile (VI).—To 4.3 g. (0.1 mole) of sodamide was added 26.2 g. (0.1 mole) of 1,1-bis-(p-chlorophenyl)-acetonitrile in dry toluene. The mixture was heated at 50° for two hours, cooled to room temperature, 11 g. (0.1 mole) of 1-dimethylamino-2-chloropropane in 50 ml. of dry toluene was added dropwise, refluxed for two hours, cooled, and then cautiously poured into cold water. The toluene layer was extracted with 6 *N* hydrochloric acid. The oily aqueous layer was made alkaline with sodium hydroxide and extracted with several portions of ether. The combined extracts were dried over anhydrous sodium carbonate, filtered, and the solvent removed *in vacuo*. The oily residue was dried in high vacuum at 80°; yield 17 g. (48%).

Anal. Calcd. for $C_{19}H_{20}Cl_2N_2$: Cl, 20.46; N, 8.07. Found: Cl, 20.26; N, 8.20.

2-(p-Chlorophenyl)-2-(p-chlorobenzyl)-4-dimethylaminopentane Nitrile (XI).—By a similar procedure, as described for VI, 28 g. (0.1 mole) of 2,3-bis-(p-chlorophenyl)-propionitrile was treated with 11 g. (0.1 mole) of 1-dimethylamino-2-chloropropane in the presence of sodamide to yield 19.5 g. (54%) of an oily residue.

Anal. Calcd. for $C_{29}H_{22}Cl_2N_2$: Cl, 19.66; N, 7.75. Found: Cl, 19.54; N, 7.84.

6-Dimethylamino-4,4-bis-(p-chlorophenyl)-heptanone-3 (VII).—To a Grignard solution prepared from 2.1 g. (0.087 mole) of magnesium, 100 ml. of ether, and 12 g. (0.11 mole) of ethyl bromide was added dropwise 15 g. (0.042 mole) of 2,2-bis-(p-chlorophenyl)-4-dimethylaminopentane nitrile in 75 ml. of dry xylene. The mixture was heated on a water-bath for three hours and to it was added 140 ml. of 6 *N* hydrochloric acid. The excess xylene was distilled, and the acidic solution was extracted with benzene. The aqueous layer was made alkaline with sodium hydroxide, extracted with ether, and the combined extracts were dried over anhydrous sodium carbonate. The solvent was removed by distillation, and the gummy residue was dried under high vacuum; yield 6.0 g. (37%).

Anal. Calcd. for $C_{21}H_{25}Cl_2NO$: Cl, 18.78; N, 3.70. Found: Cl, 18.95; N, 3.54.

The hydrochloride was prepared by dissolving 5 g. of the amino ketone (VII) in 100 ml. of anhydrous ether and then passing dry hydrogen chloride gas into this solution. The ether was removed, the gummy residue washed successively with ether and petroleum ether (30–60°), dissolved in 10 ml. of dry acetone, and precipitated with 200 ml. of anhydrous ether; m. p. 126–127°; yield 3.5 g. (65%).

Anal. Calcd. for $C_{21}H_{26}Cl_3NO$: Cl, 25.70; N, 3.38. Found: Cl, 25.58; N, 3.53.

6-Dimethylamino-4-(*p*-chlorophenyl)-4-(*p*-chlorobenzyl)-heptanone-3 (XII) was prepared by the same procedure as described for VII. From 15.2 g. (0.042 mole) of 2-(*p*-chlorophenyl)-2-(*p*-chlorobenzyl)-4-dimethylaminopentane nitrile was obtained 5.3 g. (32%) of an oily residue which analyzed correctly for the desired amino ketone.

Anal. Calcd. for $C_{22}H_{27}Cl_2NO$: Cl, 18.11; N, 3.57. Found: Cl, 18.03; N, 3.49.

The **hydrochloride** was prepared in a similar manner as described for VIII. From 4.0 g. of 6-dimethylamino-4-(*p*-chlorophenyl)-4-(*p*-chlorobenzyl)-heptanone-3 was obtained 1.1 g. (26%); m. p. 56–58°.

Anal. Calcd. for $C_{22}H_{28}Cl_3NO$: Cl, 24.76; N, 3.27. Found: Cl, 24.54; N, 3.13.

Acknowledgment.—The nitrogen and chloride determinations were carried out in our Analytical Laboratory by Mr. E. W. Post.

Summary

The chloro analogs of methadone, 6-dimethylamino-4,4-bis-(*p*-chlorophenyl)-heptanone-3 and the 6-dimethylamino-4-(*p*-chlorophenyl-4-(*p*-chlorobenzyl)-heptanone-3 were prepared.

The hydrochlorides of these compounds showed no appreciable analgesic activity.

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Studies on Furan Compounds. II. Conversion of 2-Aceto-benzofuran to 2-Methyl-3-hydroxychromone

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As is supposed, sugars represent the primary assimilation products in the vegetable kingdom, which then change under biological conditions to other important compounds. Our knowledge about the nature and intermediates of these manifold transformations is still very incomplete. It is probable that certain labile tautomeric forms of sugars, *e. g.*, furanoses, play an important part in these reactions. Since furanoses are closely related to true furan derivatives and since sugars easily give rise *in vitro* to furan derivatives, it may be assumed that eventually some of these biochemical transformations might proceed intermediately through furan compounds. In order to test this possibility, we have set as an object of our experiments the study of those transformations, which principally might take place also under biological conditions.

It was demonstrated by previous work[1] that the action of alcohols upon the *p*-toluenesulfonyl derivative of 2-acetofuranoxime results in the production of ammonium *p*-toluenesulfonate and an acetal of an unsaturated diketoaldehyde (hexen-2-dion-4,5-acetal-1). It was further shown that the corresponding saturated acetal (hexanedion-4,5-acetal-1) will be converted by acid hydrolysis to pyrocatechol, a substance which occurs in the vegetable kingdom.

The present contribution reports analogous researches, carried out on the *p*-toluenesulfonyl derivative of 2-acetobenzofuranoxime (I) in methanolic and ethanolic medium, respectively. From the methanolic reaction product, in addition to ammonium *p*-toluenesulfonate (II), three substances of entirely differing properties could be isolated. Two of them ($C_{10}H_8O_3$ and $C_8H_6O_2$) were colorless crystalline substances, the third was an almost colorless liquid ($C_{12}H_{14}O_4$) distillable *in vacuo* without decomposition. The ethanolic reaction product yielded the same crystalline substances, and in addition a liquid ($C_{14}H_{18}O_4$) having properties very similar to those of the oily compound $C_{12}H_{14}O_4$.

The constitution of the crystalline products have been established. They were found to represent 2-methyl-3-hydroxychromone (VII), a hitherto unknown substance closely related to flavonol, and 2-coumaranon[2] (*o*-hydroxyphenylacetolactone (XI)), respectively.

The correctness of the structure VII rests on the following experimental facts. The compound is very stable toward heat and acids, but decomposes on boiling with alkalies, giving rise to salicylic acid. Oxidation with hydrogen peroxide yields also salicylic acid, in addition to carbon dioxide. The formation of salicylic acid is in accordance with the chromone structure, the positive iodoform test indicates an $-O-C-CH_3$ group. The presence of a carbonyl group could not be demonstrated by the usual reagents as in the case of many other chromone and γ-pyrone derivatives. Attempts to prepare oxonium salts remained unsuccessful, too. The presence of one acidic hydroxyl group has been proved by determination of the active hydrogen, by the deep violet-blue color reaction with ferric chloride and by the formation of alkali salts and monoacyl derivatives. The fact that VII gives the corresponding methyl ether with diazomethane only in the presence of methanol, indicates, according to newer investigations by Schönberg and Mustafa,[3] a hydrogen bridge structure (VIIc). It is probable that the absence of the oxonium salt formation is partly due also to the chelate structure VIIc.

(1) Vargha, Ramonczai and Bite, THIS JOURNAL, **70**, 371 (1948).

(2) Stoermer, *Ann.*, **313**, 84 (1900).

(3) Schönberg and Mustafa, *J. Chem. Soc.*, 746 (1946).