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The Synthesis of Isomethadone

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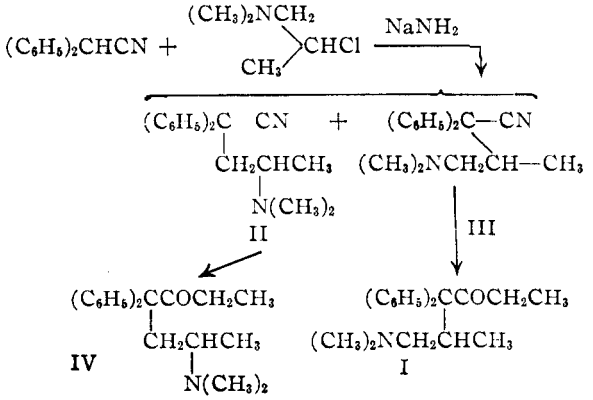
RECEIVED JUNE 23, 1952

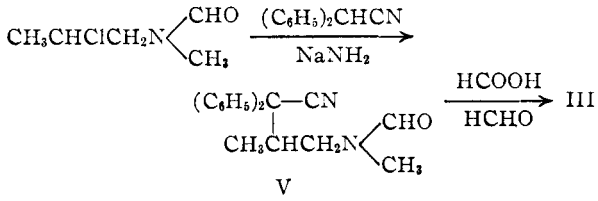
Two new and direct syntheses of isomethadone are described. In these methods diphenylacetonitrile is alkylated with 1-methylformamido-2-chloropropane and with the tosyl ester of 1-chloropropanol-2 to give, respectively, 4-methylformamido-2,2-diphenyl-3-methylbutanenitrile (IV) and 4-chloromethyl-2,2-diphenyl-3-methylbutanenitrile (VIII). These nitriles are readily converted into isomethadone.

In view of the importance of isomethadone (I), 6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone, as an analgesic,[1] it was of interest to investigate simpler methods of synthesis. Hitherto, isomethadone has been prepared only as a by-product of the methadone synthesis and, in fact, major attention has been devoted to the synthesis of the latter at the expense of its isomer.[2] In this synthesis, diphenylacetonitrile is alkylated with 1-dimethylamino-2-chloropropane giving rise to a mixture of 2,2-diphenyl-4-dimethylaminovaleronitrile (II) and 4 - dimethylamino - 2,2 - diphenyl - 3 - methylbutyronitrile (III). The isomeric nitriles are converted to methadone (IV) and isomethadone, respectively, by reaction with ethylmagnesium bromide. The formation of the two nitriles in the alkylation reaction is believed to be due to the cyclic quaternary structure of the alkylating agent.[3]

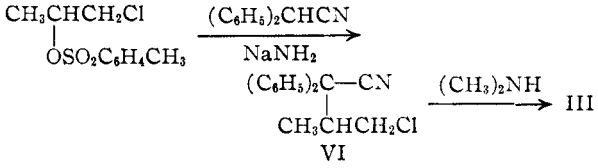


Two new syntheses of isomethadone have been realized. In the first, diphenylacetonitrile is alkylated with 1-methylformamido-2-chloropropane which reacts normally in displacement reactions. The resulting formamide V is readily reduced with a mixture of formic acid and formaldehyde to the desired butyronitrile III.

The second approach utilizes the greater reactivity of a secondary tosyl ester in comparison with a primary chlorine atom in alkylation reactions. Thus, in the alkylation of diphenylacetonitrile with the tosyl ester of 1-chloropropanol-2



using sodamide in toluene 4-chloromethyl-2,2-diphenyl-3-methylbutanenitrile (VI) is formed in at least 65% yield. No isomeric nitrile could be isolated from the reaction mixture. The chloro compound VI was readily converted to the desired nitrile III by reaction with dimethylamine at 150°.



Two other sulfonic esters of 1-chloro-2-propanol were used in the alkylation of diphenylacetonitrile. The benzenesulfonyl and the methanesulfonyl esters gave, respectively, 60 and 53% yields of the chlorobutyronitrile VI.

The preparation of the chloronitrile VI by alkylation of diphenylacetonitrile with 1-chloro-2-bromopropane was reported previously[4] in good yields (70%). However, the reaction of this compound with morpholine to give the corresponding morpholinobutyronitrile proceeded poorly (18% yield).

The identity of the butyronitrile III obtained from these syntheses was established by comparing melting points of the picrates and the *p*-toluenesulfonates with authentic samples and by examination of infrared spectra. Identity was further confirmed by conversion to isomethadone.

Acknowledgment.—The authors wish to express their thanks to Dr. Nelson Trenner for the infrared absorption data, to Mr. Richard Boos for the analytical data, and to Messrs. William Martin and Henry W. Johnson for technical assistance.

Experimental

All melting points are uncorrected.

1-Methylformamido-2-propanol.—A mixture of 89 g. of 1-methylamino-2-propanol and 180 g. of formamide was heated with stirring at 150–160° for 3 hours. The mixture was cooled and fractionated using a Vigreux column. The first fraction boiling at 63–71° (1 mm.) and weighing 136.0 g. was practically pure formamide. The second and third fractions boiled at 90–92° (5 mm.). The yield was 109.4 g. (93%), $n^{23}D$ 1.4665.

Anal. Calcd. for $C_5H_{11}O_2N$: C, 51.28; H, 9.40; N, 11.96. Found: C, 51.18; H, 9.64; N, 11.91.

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(2) Office of Publications Board, Dept. of Commerce, Report P. B. 981, p. 96-A; E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL, **69**, 188, 2454 (1947); N. R. Easton, J. H. Gardner and J. R. Stevens, *ibid.*, **69**, 976 (1947), **70**, 76 (1948); R. H. Thorp, E. Walton and P. Ofner, *Nature*, **159**, 679 (1947); E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949).

(3) W. R. Brode and M. W. Hill, THIS JOURNAL, **69**, 724 (1947). E. M. Schultz and J. M. Sprague, *ibid.*, **70**, 48 (1948); A. A. Larsen; B. F. Tullar, B. Elpern and S. S. Buck, *ibid.*, **70**, 4194 (1948); L. C. Cheney, R. R. Smith and S. B. Binkley, *ibid.*, **71**, 55 (1949).

(4) J. Attenburrow, J. Elks, B. A. Hems and K. N. Speyer, *J. Chem. Soc.*, 516 (1949).

1-Methylformamido-2-chloropropane.—To a solution of 109.4 g. of 1-methylformamido-2-propanol dissolved in 235 cc. of dry chloroform and 56.4 g. of dry pyridine was added with stirring 89.6 g. of thionyl chloride over a period of 30 minutes, keeping the temperature below 73°. The reaction mixture was maintained at 73° for 10 hours and then cooled to room temperature. The mixture was washed with saturated sodium chloride solution and then with saturated sodium bicarbonate, and finally with water. The organic layer was dried over sodium sulfate, the solvent removed *in vacuo* and distilled; yield 77 g. (79%), b.p. 139–141° (58 mm.), $n^{22.5}D$ 1.4699.

Anal. Calcd. for $C_5H_{10}ClNO$: C, 44.28; H, 7.40; N, 10.33; Cl, 26.15. Found: C, 44.49; H, 7.70; N, 10.28; Cl, 25.88.

4-Methylformamido-2,2-diphenyl-3-methylbutanenitrile (V).—To a solution of 19.3 g. of diphenylacetonitrile dissolved in 40 cc. of xylene was added 3.9 g. of sodamide slurried in 35 cc. of xylene. The mixture was heated with stirring under a nitrogen atmosphere to 105–110° until the quantitative amount of ammonia had been liberated. The temperature of the reaction mixture was brought to 30° and 0.27 g. of sodium iodide added, followed by the dropwise addition over a period of 15 minutes of 6.8 g. of 1-methylformamido-2-chloropropane. During the addition the temperature rose to 35°. The reaction mixture was heated to 110–115° for 3 hours, cooled to room temperature and extracted with water. The aqueous solution was extracted with benzene. The organic layers were combined, filtered from a small amount of insoluble material and concentrated to dryness *in vacuo*. The residue was dissolved in 100 cc. of ether and cooled overnight at 5–10° to obtain a crystalline product, 8.4 g. (57.5%), m.p. 127.5–129°. For analysis the product was recrystallized from butanol.

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84; N, 9.63. Found: C, 78.31; H, 7.06; N, 9.68.

4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile (III).—Two grams of trioxane, 6.0 g. of formic acid (98–100%) and 5.84 g. of formamido compound (V) were heated under reflux for 112 hours. At the end of this time a drop of the reaction mixture when added to an excess of water gave a clear solution, indicating a complete reaction. The mixture was cooled to 25°, poured into 100 cc. of water and made basic with concd. ammonia. The product which separated crystallized completely on standing overnight. The yield was 5.1 g. (91%), m.p. 63–64.5°. Recrystallization from petroleum ether gave a solid melting at 65.5–66.5°. A mixed melting point with an authentic sample of m.p. 65.5–66.5° gave no depression. The picrate, m.p. 210–211°, and *p*-toluenesulfonate, m.p. 222–224°, were also synthesized. The mixed melting points of both salts with authentic samples showed no depression.

Anal. Calcd. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.01. Found: C, 81.70; H, 7.82; N, 10.16.

***p*-Toluenesulfonate of 1-Chloro-2-propanol.**—To a mixture of 190.6 g. of *p*-toluenesulfonyl chloride and 158.2 g. of pyridine cooled to 0°, 94.6 g. of propylene chlorohydrin was added with stirring over a period of 20 minutes. Stirring at 0° was continued for 1 hour and the reaction mixture placed in the ice-box overnight. The reaction mixture was stirred at room temperature for 24 hours. The precipitated pyridine hydrochloride was then filtered off. Ten cubic centimeters of water was added to the cooled filtrate and it was then allowed to stand for 1 hour. The reaction mixture was diluted with 300 cc. of ether or benzene, washed successively with 2.5 *N* HCl, water, 1 *N* sodium hydroxide and finally with water. The washed solution was dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the crude ester was distilled, b.p. 119–120° at 0.05 mm.; yield 227 g. (91%).

Anal. Calcd. for $C_{10}H_{13}O_3ClS$: Cl, 14.26. Found: Cl, 13.9.

In a similar manner the esters of benzenesulfonic acid (yield 87%, b.p. 105–106° (0.1 mm.)) and methanesulfonic acid (yield 75%; b.p. 76–77° (0.4 mm.)) were prepared.

4-Chloromethyl-2,2-diphenyl-3-methylbutanenitrile (VI).—Diphenylacetonitrile, 101 g., was dissolved in 800 cc. of dry toluene and added to a slurry of 20.3 g. of sodamide in 200 cc. of dry toluene. The mixture was heated with stirring to 106° under nitrogen. Heating and stirring was continued until 95% or more of the theoretical amount of ammonia was evolved. The reaction mixture was cooled to 65°, and 130 g. of *p*-toluenesulfonate ester VII was added slowly with stirring keeping the temperature below 80°. The reaction mixture was heated at reflux with stirring for 18 hours, cooled to room temperature and poured into 500 ml. of water. The organic layer was washed with water, dried over anhydrous magnesium sufate, and concentrated *in vacuo*. The residue was distilled, b.p. 119–124° (0.1 mm.); yield, 160 g., 65%.

Anal. Calcd. for $C_{17}H_{16}NCl$: C, 75.68; H, 5.98; N, 5.19. Found: C, 75.68; H, 5.90; N, 5.33.

4-Dimethylamino-2,2-diphenyl-3-methylbutanenitrile (III).—A Carius bomb tube was charged with 25 g. of the chloronitrile VIII, 25 cc. of anhydrous dimethylamine and 0.5 g. of copper sulfate. The sealed tube was heated for 48 hours at 150°. The reaction mixture was cooled to room temperature and extracted with benzene. The benzene extract was washed with water and then extracted with 2.5 *N* HCl. The acidic extracts were made alkaline and extracted with benzene. The benzene extracts were concentrated *in vacuo* to an oil which crystallized on standing; yield 14.5 g. (58%). Recrystallization from petroleum ether gave a solid which melted at 65.5–66.5°. The hydrochloride melted at 218–220°. A mixed melting point with an authentic sample of the nitrile hydrochloride melted at 218–220°.

A comparison of the infrared spectra of the nitrile hydrochloride with an authentic sample confirmed the identity of the two compounds.

Anal. Calcd. for $C_{29}H_{22}N_2 \cdot HCl$: C, 72.48; H, 7.36; N, 8.90. Found: C, 72.34; H, 7.24; N, 9.09.

6-Dimethylamino-4,4-diphenyl-5-methyl-3-hexanone (I).—Compound III synthesized from synthetic approaches discussed above was converted to isomethadone by orthodox procedure[3] and identified by comparison with derivatives synthesized from an authentic sample. A discussion of the preparation of derivatives is given by Easton, *et al.*[2] The following is a tabulation of data.

The melting point of the picrate was 149–150°. A mixed melting point with an authentic sample showed no depression. The melting point of methiodide was 263–264°. The mixed melting point with an authentic sample exhibited no depression.

Anal. Calcd. for the monohydrate hydrochloride $C_{21}H_{28}NOCl \cdot H_2O$: C, 69.38; H, 8.31; N, 3.87. Found: C, 69.55; H, 8.28; N, 4.03.

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