

NEW METHOD OF SYNTHESIZING MOLINDONE
AND ITS ANALOGS

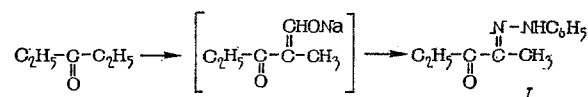
V. I. Shvedov, L. B. Altukhova,
and A. N. Grinev

UDC 615.214.32.012.1

Recently, interest has been renewed in derivatives of 3-acetylpyrrole and 4-ketotetrahydroindole as compounds with a marked effect on the central nervous system [1]. In addition, the Mannich bases of these derivatives possess antidepressive properties. Thus, for example, the medicinal compound molindone (2-methyl-3-ethyl-4-keto-4,5,6,7-tetrahydro-5-morpholinomethylindole) is a highly effective neuroleptic and antipsychotic agent similar to chlorpromazine [2, 3]. However, the synthesis of derivatives of pyrrole and ketotetrahydroindole, usually accomplished by the Knorr method based on the isonitroso derivatives of dicarbonyl compounds, often results in low yield; and the preparation of the nitroso derivatives themselves is accompanied in a number of cases with a whole series of difficulties [4, 5]. Isonitrosopentanone, which is used in the synthesis of molindone, is, for example, obtained in low yield by the nitrosation of diethylketone with amyl nitrite [6].

We found that substituted pyrroles, as a rule, can be obtained in a higher yield if the monophenylhydrazones of the α -dicarbonyl compounds are used for the reaction instead of the isonitroso ketones. The presently known methods of synthesizing the 2-phenyl-hydrazone of pentanedione-2,3 (I), which we decided to use as the starting compound to synthesize molindone, do not have practical value. When phenylhydrazine reacts with acetylpropionyl acetate, a mixture of the phenylhydrazones of pentanedione-2,3 is formed [7]. Using 2-mercapto-3-pentanone. I can be obtained with a yield of only 20% [8]. The comparative unavailability of the raw material and low yield of the final product are drawbacks of these methods.

We propose a preparative method of synthesizing I. When ethyl formate is reacted with diethylketone in the presence of sodium alcoholate, the sodium derivative of 2-methylpentanal-1-one-3 is obtained, which is coupled with phenyldiazonium chloride as an aqueous-alcoholic solution without isolating it. The employment of a symmetrical ketone for the reaction makes it possible to eliminate the formation of isomeric compounds and leads to the preparation of I with a 90% yield.

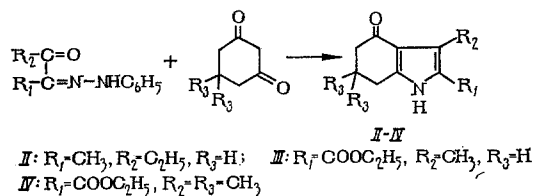


When a mixture of I and cyclohexanedione-1,3 is treated with zinc dust in acetic acid, 2-methyl-3-ethyl-4-keto-4,5,6,7-tetrahydroindole (II), the starting compound in the synthesis of molindone, is formed with a 60% yield. Cyclohexanedione-1,3 N-phenylimine, which is formed as a by-product, is easily removed from the principal substance by recrystallization from acetone.

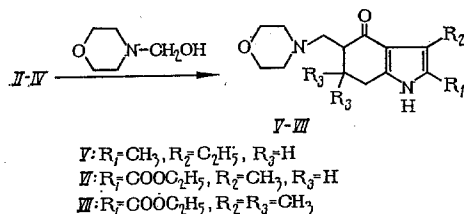
Similarly, the ketotetrahydroindole derivatives (III, IV) which we used as the starting compounds in the synthesis of analogs of molindone, were obtained from phenylazoacetoacetic ester and cyclohexanedione-1,3 or dimedone.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow.
Translated from *Khimiko-Farmatsevticheskii Zhurnal*, Vol. 6, No. 9, pp. 29-31, September, 1972. Original article submitted June 24, 1971.

© 1973 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for \$15.00.



The reaction of II-IV with N-methylmorpholine in acetic acid results in the formation of the crystalline Mannich bases V-VII. One of them, V, is known as molindone.



EXPERIMENTAL

2-Phenylhydrazone of Pentamedione-2,3 (I). To a cooled mixture of 25.8 g of diethylketone and 33.3 g ethyl formate with good agitation was added in small portions a methanolic solution of sodium methylate prepared from 6.9 g of sodium and 70 ml of methanol. The reaction mixture was allowed to stand overnight. The sodium derivative of 2-methylpentanal-1-one-3 formed was dissolved in a minimum amount of water, and it was slowly added at 0-5°C to a solution of phenyldiazonium chloride prepared in the usual way from 23.3 g of aniline, 17.3 g of sodium nitrite, and 75 ml of concentrated hydrochloric acid, all of which was then brought to pH 5.0-6.0 with sodium acetate. The precipitate formed was filtered off, washed with cold water, and dried. The yield of I was 42.8 g (90%), mp 105-106°C. Found %: C 69.07; H 7.48; N 14.64. C₁₁H₁₄N₂O. Calculated %: C 69.44; H 7.41; N 14.72.

2-Methyl-3-ethyl-4-keto-4,5,6,7-tetrahydroindole (II). A mixture of 11.2 g of cyclohexanedione-1,3, 9.5 g of I 5 g of fused sodium acetate, and 100 ml of acetic acid was heated to 60°C, then 20 g of zinc dust was added in portions to it over a 15 min period. The reaction mixture was boiled 1 h, the colorless solution was decanted, and the sediment was washed with hot acetic acid (3 × 30 ml). The combined acetic solutions were poured into 1 liter of cold water, the precipitate formed was filtered off. The mixture of substances obtained was dissolved with heat in acetone and cooled. The precipitate of cyclohexanedione-1,3 N-phenylimine was filtered off. The mother liquor was diluted with water and the crystals which precipitated were isolated. The yield of II was 5.3 g (60%), mp 182-183°C (from benzene). Found %: C 74.55; H 8.58; N 7.81. C₁₁H₁₅NO. Calculated %: C 74.53; H 8.53; N 7.90. Compounds III and IV were similarly prepared.

2-Carboethoxy-3-methyl-4-keto-4,5,6,7-tetrahydroindole (III). The yield was 65%, mp 167-168°C. According to the literature [1], the mp is 163-164°C.

2-Carboethoxy-3,5,5-trimethyl-4-keto-4,5,6,7-tetrahydroindole (IV). The yield was 51.5%, mp 169-170°C. Found %: C 67.60; H 7.44; N 5.76. C₁₄H₁₉NO₃. Calculated %: C 67.44; H 7.68; N 5.62.

Mannich Bases. To a solution of 0.01 mole of ketone in 30 ml of acetic acid at 60-70°C and with agitation was added dropwise 0.015 mole of N-methylmorpholine; the reaction solution was stirred for 5 h at this same temperature. The reaction mixture was diluted with water and filtered free of the unreacted starting compound. The filtrate was made alkaline with aqueous ammonia while cooling, the precipitate was isolated, and dissolved in 25 ml of 0.5 N hydrochloric acid. The solution obtained was filtered once more and while stirring and with cooling, a cold aqueous ammonia solution was added dropwise to it. The Mannich base precipitated in the form of colorless needles.

2-Methyl-3-ethyl-4-keto-5-morpholinomethyl-4,5,6,7-tetrahydroindole (V). The yield was 50%, mp 104-105°C. According to the literature [9], the mp is 104°C.

2-Carboethoxy-3-methyl-4-keto-5-morpholinomethyl-4,5,6,7-tetrahydroindole (VI). The yield was 87%, mp 174-175°C. Found %: C 63.79; H 7.56; N 8.66. C₁₇H₂₄N₂O₄. Calculated %: C 63.73; H 7.55; N 8.74.

2-Carbethoxy-3,5,5-trimethyl-4-keto-5-morpholinomethyl-4,5,6,7-tetrahydroindole (VII). The yield was 60%, mp 145-146°C. Found %: C 65.42; H 8.01; N 7.98. $C_{19}H_{28}N_2O_4$. Calculated %: C 65.49; H 8.09; N 8.04.

LITERATURE CITED

1. R. Moffett, *J. Med. Chem.*, **11**, 1251 (1968).
2. Belgian Patent No. 670798; *Chem. Abstr.* **65**, 7148 (1966).
3. S. Hauptmann, *Z. Chem.*, **6**, 107 (1966).
4. A. Treibs and D. Dinelli, *Justus Liebigs. Ann. Chem.*, **517**, 152 (1935).
5. *Organic Reactions* [in Russian], Vol. 7, Moscow (1963), p. 438.
6. L. Claisen and O. Mannasse, *Ber. Dtsch. Chem. Ges.*, **22**, 526 (1889).
7. H. Pechmann, *Ibid.*, **21**, 1411 (1888).
8. F. Asinger, M. Thiel, and H. Portatius, *J. Prakt. Chem.*, **6**, 81 (1958).
9. S. Hauptmann and M. Martin, *Z. Chem.*, **8**, 334 (1968).