METHODS OF DRUG SYNTHESIS AND PRODUCTION TECHNOLOGY

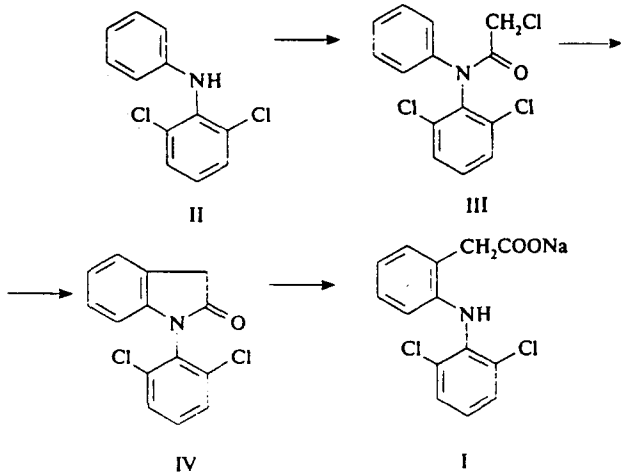
AN ADVANCED METHOD FOR THE PREPARATION OF 2,6-DICHLORODIPHENYLAMINE AND ITS N-CHLOROACETYL DERIVATIVE — INTERMEDIATES IN THE SYNTHESIS OF ANTIINFLAMMATORY DRUG ORTOPHENUM

S. Yu. Ryabova,[1] A. I. Bokanov,[1] I. P. Isakovich,[1] V. A. Kuzovkin,[1] N. B. Grigor'ev,[1] V. I. Levina,[1] V. I. Shvedov,[1] and V. G. Granik[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 1, pp. 36 – 38, January, 1996.

Original article submitted September 17, 1995.

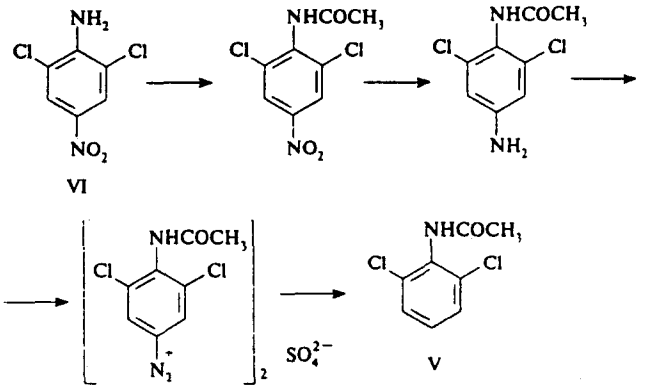
It is known that 2,6-dichlorodiphenylamine (II) is the main intermediate in the synthesis of ortophenum (I) (voltaren, diclofenac sodium) [1]. Compound II is used to prepare I by N-chloroacetylation to obtain III, which is subjected to Friedel – Crafts cyclization. The obtained 1-(2,6-dichlorophenyl)indolin-2-one (IV) is then subjected to alkaline hydrolysis to yield I.



II III IV I

The industrial synthesis of II uses the high-temperature (160 – 170°C) Ullman condensation of bromobenzene and 2,6-dichloroacetanilide (V) [2], which takes a rather long time (> 30 h). The following shortcomings of this process are substantial:

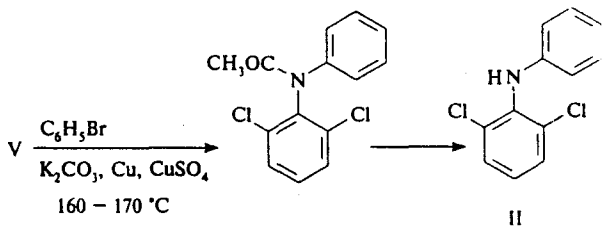
(1) The starting compound itself is a product of complex synthesis:



VI V

and the yield of V, as calculated for 2,6-dichloro-4-nitroaniline (VI), is only 26%.

(2) The yield of intermediate II, which is obtained according to the scheme below,



is rather low (63%, as calculated for V).

(3) The entire technological procedure is rather complex: using powdered copper requires safety measures to be taken

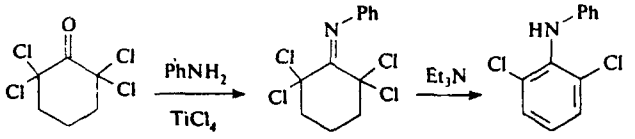
[1] Chemical Drugs Center—All-Russia Research Institute of Pharmacological Chemistry, Moscow, Russia.

0091-150X/96/3001-0038$15.00

because hydrogen is evolved during the synthesis; excess bromobenzene is distilled of with live steam; and, as mentioned above, the reaction requires a high temperature and takes a long time.

(4) During the Ullman condensation, bromine is partially substituted for one of chlorine atoms in compound V. As a result, the product (II) contains an impurity of 2-chloro-6-bromodiphenylamine [3] contaminating compound I.

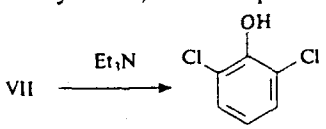
Recently, Saeki et al. [3] reported the synthesis of compound II by condensation of 2,2,6,6-tetrachlorocyclohexane (VII)[2] with aniline in the presence of titanium tetrachloride and subsequent dehydrochlorination of the obtained tetrachloroanil (VIII) to yield target compound II [3].



VII VIII II

The most favorable ratio between the reagents was reported to be VII : aniline : $TiCl_4$ = 1 : 4 : 1.1 [3]. Note that intermediate VIII is obtained as a black compound, and its subsequent dehydrochlorination requires that it be subjected to special purification.

During the development of an industrial process for the manufacture of ortophenum using this scheme, we performed the procedure described in the patent [3] and found that under the conditions specified there the yield of intermediate VIII does not exceed 65%. Using gas chromatography and polarography, we analyzed the technical unpurified product VIII and the mother liquors obtained after its recrystallization. It was found that the technical product VIII contained about 16% of compound VII and its content in the mother liquors amounted to 50 – 65%. This suggests that the yield of compound VIII reported in the patent (calculated for 100% product) is significantly overestimated. We demonstrated experimentally that the product VIII obtained under the conditions described in [3] cannot be used in the subsequent stage. Because of a rather large contaminating amount of the initial compound, in addition to the target compound II, the dehydrochlorination also yields 2,6-dichlorophenol (IX).



IX

It is rather difficult to separate this impurity IX, whereas its presence leads to contamination of product I during the other stages. Having studied the synthesis of dichlorodiphenylamine II reported in [3], we came to the conclusion that the ketone : aniline : catalyst = 1 : 4 : 1.1 ratio, which was claimed to be the most favorable, is not optimal.

We started with considering the role of $TiCl_4$ catalysts in the formation of anil VIII. It is known [5 – 7] that $TiCl_4$ forms complexes with amines and other organic compounds, ketoimines in particular. Therefore, we assumed that a complex between $TiCl_4$, aniline, and ketone VII forms in the course of the condensation. In this complex, the carbonyl group of the ketone lies sterically close to the amine group of aniline; this feature promotes the formation of anil VIII. Apparently, the ability of $TiCl_4$ to form complexes with the initial and the final compounds provides the driving force for the reaction (the reaction of ketone VII with aniline is reversible). Therefore, the minimum ratio between the ketone and $TiCl_4$ must be 1 : 1.5 (another 0.5 mole of $TiCl_4$ is required to bind the water liberated during the reaction). Obviously, to change the VII : $TiCl_4$ ratio, we had to study the effects related to variation of the VII : $TiCl_4$ ratio, because, when excess $TiCl_4$ is decomposed with water after the completion of reaction, a large amount of hydrochloric acid, which can decompose anil VIII to the initial components, is liberated. We found the optimum amount of aniline to be 5.5 – 7 mole per mole of ketone VII. Such excess is required not only to bind the HCl liberated during the reaction as a result of the decomposition of the reaction mass by water, but also to buffer the aqueous layer. In this way, the hydrolysis of anil VIII at the water – toluene interface (see Experimental part) was evaded. The fact that the ratio between the reagents in the described procedure is optimum is confirmed by the data of gas chromatographic and polarographic analyses: technical anil VIII obtained according to the procedure described in this paper contained 0.7 – 1.4% of ketone VII (against ~ 16% reported in [3], see above).

It is noteworthy that the fact that aniline is taken in a larger excess presents no additional difficulties, because it is easily regenerated with 81 – 84% yield by treating the mother liquor with alkali. Another technological improvement in the preparation of anil VIII involved an increase in the amount of solvent (toluene) used. This makes it possible to obtain a more uniform suspension and, as a result, attain higher conversion in the condensation and solve the problem of transporting the reaction mass. Thus, we obtained an intermediate product VIII of high purity (according to polarographic data, the content of target product amounts to 92 – 99%) with an almost quantitative yield [8]. As a result, there was no need to purify anil VIII, which was subjected to dehydrochlorination as obtained (conditions: dimethylformamide, triethylamine, 5 h at 95 – 100°C). The yield of the target product II was higher than 90%, and its purity was higher than 98% (according to gas chromatography). It is important that, according the procedure described here, there is no need to isolate compound II and purify it prior to chloroacetylation; there is also no need to distill off DMF completely, because a chloroacetylated derivative of high quality can be obtained with a high yield even at a DMF content of ~ 25%.

[2] A technologically convenient procedure for the preparation of tetrachloroketone (VII) was described in [4].

EXPERIMENTAL PART

Compound VIII was determined by polarography at a constant current with an OH-105 (Hungary) polarograph. The other parameters of polarographic measurements were the same as described in [9].

The analysis rests on the reaction of consecutive scission of C–Cl bonds. Compound VIII can be determined in the presence of VII because for VII this reaction is very slow in aqueous solutions.

The solution for polarographic measurements contained about 0.0001 g/ml of compound VIII in a mixture of equal volumes of 0.01 M borate buffer solution (pH 9.18) and ethyl alcohol. A polarographic curve was recorded from 0.0 V to – 1.0 V (with a silver reference electrode). For calculations, which were performed according to the standard potentials method, the current measured at – 0.45 V was used.

Gas chromatographic analyses were carried out with a Carlo Erba (Vega series 2) instrument equipped with a flame ionization detector using a 1-m-long column with an inner diameter of 3 mm. The column was packed with NHMDS chromaton with 5% OV-17. The analysis of HMDS – dichlorodiphenylamine II was conducted in the programmed temperature mode: $T_{initial}$ = 125°C, heating at 10°C/min, T_{final} = 235°C. The final temperature was maintained for 15 min. The analysis of chloroacetyl derivative III was conducted in an isothermal mode at 245°C.

N-Phenyl-2,2,6,6-tetrachlorocyclohexaneimine (VIII). To a solution of VII (15 g, 60 mmole) [4] in 150 ml of toluene, 17 g (90 mmole) of $TiCl_4$ was added. The mixture was cooled to 10°C and aniline (36.4 g, 360 mmole) was added dropwise over 1.5 h so that the temperature would not exceed 20°C. The mixture was left to stand at this temperature for 2 h. Then, 90 ml of water cooled to 10°C was added, and the mixture was stirred until the reaction mass was completely dissolved. The organic and aqueous layers were then separated. The organic layer was evaporated to yield VIII (19.6 g, 99%) as a yellow oil, which solidifies on cooling.

Pure N-phenyl-2,2,6,6-tetrachlorocyclohexaneimine is a yellow crystalline powder; m.p. 70.5 – 71.5°C according to [3]. Imine VIII of 92 – 99% purity (according to polarographic data) was used without further purification to prepare II.

2,6-Dichlorophenylamine (II). A mixture of imine VIII (19.54 g, 63 mmole), DMF (98 ml). and triethylamine (19.5 ml, 140 mmole) was heated at 95 – 100°C for 5 h. The mixture was cooled, triethylamine hydrochloride was separated by filtration and washed with DMF. The filtrate was evaporated. The residue (10.5 g) was a brown oil, which contained 25% of DMF (according to gas chromatography). Without taking into account the solvent, the final product contained 94.7% of the target compound. Pure 2,6-dichlorodiphenylamine is a white crystalline substance; m.p. 49 – 51°C according to [2]. Dichlorodiphenylamine as an oil of 94 – 99% purity (ignoring the content of DMF) was used without further purification to prepare III.

N-Chloroacetyl-2,2-dichlorodiphenylamine (III). A mixture of compound II as an oil (10.5 g) and chloroacetyl chloride (4.32 g, 54 mmole) was slowly heated to 108 ± 2°C with stirring. The mixture was left at this temperature for 2 h. The heating was then stopped. At 105°C, 10 ml of toluene was added, taking care to maintain the temperature at 80 – 83°C. Then, 14 ml of isopropyl alcohol was added, and the reaction mixture was boiled for 1 h. The reaction mass was cooled to 5 ± 2°C and left to stand at this temperature for 2 h. The precipitate was filtered off, washed with 21 ml of isopropyl alcohol, and dried to yield 8.7 g (86%) of compound III; m.p. 145.5 – 146.5°C (from isopropyl alcohol). The purity of compound III was 99% (according to gas chromatography). The published melting point, 144 – 148°C (with an accuracy of 2°C) [2].

2,6-Dichlorophenol (IX). A mixture of compound VII (6.45 g, 27 mmole), DMF (30 ml), and triethylamine (8.6 ml, 61 mmole) was heated at 100°C for 4 h. It was then cooled, and triethylamine hydrochloride was separated by filtration. The filtrate was evaporated. The residue was mixed with 25 ml of water, and 1 N KOH was added to bring the pH to alkaline according to acid – base indicator. The aqueous solution was separated from resinous matter, mixed with activated carbon, and filtered. The clarified transparent solution was acidified with a dilute HCl (1 : 10) solution. The formed precipitate was separated by filtration, washed with water, and dried to yield compound IX (1.3 g, 30%); m.p. 64°C, M^+ 161, $C_6H_4Cl_2O$, M 161, published [10] m.p. 64 – 65°C.

Regeneration of aniline. An aqueous layer left after the preparation of imine VIII (90 ml) was cooled to +10°C and 24 ml of 40% NaOH in 220 ml of water (pH 9 – 10) was added. The TiO_2 precipitate was separated by filtration. The precipitate was mixed with 60 ml of toluene, again separated by filtration, and washed with toluene (2 × 25 ml).The aqueous mother solution and the washing filtrate were placed in a separating funnel and shaken. The layers were separated. The toluene extract was evaporated to yield 25 ml (25.6 g; 84.6%) of aniline of 92% purity (according to gas chromatography).

REFERENCES

1. M. D. Mashkovskii, *Drug Preparations* [in Russian], Vol. 1, Meditsina, Moscow (1984).
2. *Manufacture of Ortophenum, Industrial Process Description* [in Russian], LPBO Latvbiofarm (1988).
3. T. Saeki, H. Yshikawa, and T. Oki, *Eur. Patent Appl.* 0 313 740-A2 (Int. Cl. C 07 C 119/06, C 07 C 87/60, C 07 C 85/100), 1988; *Chem. Abstr.*, **III:p**, 173731c.
4. Yu. I. Laz'yan, A. I. Bokanov, V. A. Kuzovkin, et al., *Khim.-Farm. Zh.*, **28**(12), 52 – 54 (1994).
5. C. Sasaki, K. Nakajima, M. Kojima, et al., *Bull. Chem. Soc. Jpn.*, **64**(4), 1318 – 1324 (1991).
6. G. W. A. Fowles and R. A. Hoodles, *J. Chem. Soc.*, No. 1, 33 – 38 (1963)
7. D. Schwartz and D. Naegli, *Inorg. Nucl. Chem. Lett.*, **2**(6), 149 – 152 (1996).
8. S. Yu. Ryabova, A. I. Bokanov, I. P. Isakovich, et al., *Russ. Patent Application* No. 92002661 / 04, 13.03.95.
9. S. G. Mairanovskii, Ya. P. Stradyn', and V. D. Bezuglyi, *Polarography in Organic Chemistry* [in Russian], Moscow (1975).
10. E. C. Gilbert, R. E. Jones, D. C. Maheen, et al., *Ind. Eng. Chem.*, Prod. Res. Dev., **14**(1), I – II (1975).