SYNTHESIS AND STEREOCHEMISTRY OF 5-SUBSTITUTED QUINUCLIDINE-2-CARBOXYLIC ACIDS WITH SEMICYCLIC DOUBLE BONDS

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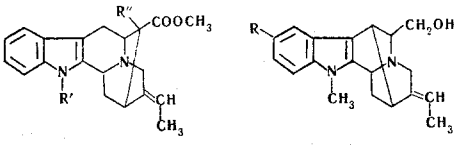
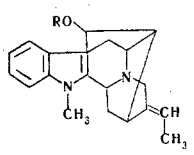
Esters of 5-methylene- and 5-ethylidenequinuclidine-2-carboxylic acid were synthesized using the Wittig reaction. Using NMR spectra, the stereochemistry of the 5-substituted quinuclidine-2-carboxylic acids with semicyclic double bonds was studied.

Derivatives of quinuclidine-2-carboxylic acid with ethylidene groups in the 5 position constitute part of the molecule of the naturally occurring macusine alkaloid series. The correspondingly substituted quinuclidines with semicyclic double bonds are of interest as possible intermediates for the synthesis of other groups of alkaloids—sarpagine, lochnerine, tetraphyllicine, rauvomitine, etc.:



R′ = H; R″ = CH_2OH- macusine R = H-lochnerine
R′ = CH_3 R″ = CH_2OH-voachalotine R = OH-sarpagine

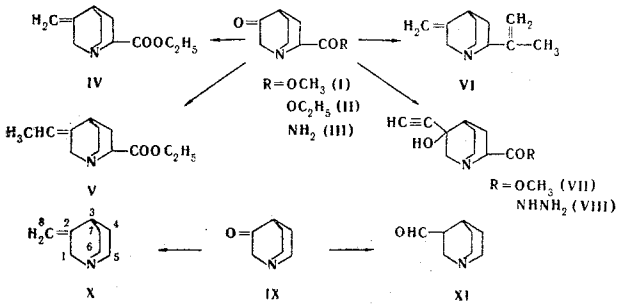


R = H-tetraphyllicine
R = $(CH_3O)_3C_6H_2CO$-rauvomitine

However, up to the present there has been no information whatever on the synthesis of compounds of this series.

An extention of our previously reported method for obtaining 5-oxoquinuclidine-2-carboxylic acids [1] based on 3-quinuclidone, introducing various substituents in the β-position of the quinuclidine ring by the Wittig reaction [2, 3], allows the synthesis of 5-substituted quinuclidine-2-carboxylic acids and, in particular, compounds with semicyclic double bonds. In the synthesis of quinuclidine-2-carboxylic acid having methylene and ethylidene groups in the 5 position, the reaction between 5-oxoquinuclidine-2-carboxylic ester and, respectively, triphenylmethylene- and triphenylethylidenephosphoranes was used.

A comparison of the reactivities of 3-quinuclidone (IX) and 5-oxoquinuclidine-2-carboxylic esters (I–II) in the Wittig reaction showed that the introduction of an α'-ester group caused a marked decrease in the reactivity of the β-keto group in the quinuclidine nucleus. While 3-methylenequinuclidine (X)* is obtained from 3-quinuclidone by the Wittig reaction in a 67.2% yield, the analogous procedure with methyl 5-oxoquinuclidine-2-carboxylate (I) gives (after supplementary esterification) only 13.5% of the methylene ester (IV); more than 40% of the material is recovered as the keto ester II. While the reaction of triphenylethylidenephosphorane with 3-quinuclidone, as we have shown previously [3], gives a 71% yield of 3-ethylidenequinclidine, the yield of ethyl 5-ethylidenequinuclidine-2-carboxylate in the analogous reaction is 48.1% (about 20% of the starting material is recovered as the keto ester II).



The decrease in the reactivity of the keto group in 5-oxoquinuclidine-2-carboxylic esters in comparison with 3-quinuclidone is also observed in the ethynylation reaction. As has been shown previously [4], the reaction of 3-quinuclidone with sodium acetylide gives 3-hydroxy-3-ethynylquinuclidine in a 64% yield. The analogous reaction in the case of methyl 5-oxoquinuclidine-2-carboxylate I gives a yield of only 15.8% of methyl 5-hydroxy-5-ethynyl-2-carboxylate (VII). More than 40% of the starting material I is recovered as the keto ester I and the product of its ammonolysis—5-oxoquinuclidine-2-carboxamide (III).

It is interesting to note that in view of the decreased reactivity of the keto group of the 5-oxoquinuclidine-2-carboxylic esters, the stability of the ylenes of the phosphorus components acquires particular importance. Thus, for instance, triphenylmethylenephosphorane is less stable than triphenylethylidenephosphorane. As a result, the yield of V in the same type of Wittig reaction is significantly higher than the yield of IV. The even less stable methoxymethylenetriphenylphosphorane, which reacts readily and in high yield with 3-quinuclidone, giving 3-formyl-quinuclidine [5] is practically completely decomposed before it reacts with the 5-oxoquinuclidine-2-carboxylate esters.

At the same time, the reduced reactivity of the keto group in the 5-oxoquinuclidine-2-carboxylic esters creates the possibility for side reactions.

*See footnote on following page.

Besides the ketonic carbonyl, in this case, the ylene also adds to the carbonyl group of the ester moiety. Thus, for instance, by the reaction of I with triphenylmethylenephosphorane, together with ethyl 5-methylenequinuclidine-2-carboxylate, readily undergoing saponification in an acid medium, nitrogen-containing compounds that did not undergo saponification was obtained. Analysis of the "unsaponifiable" products by gas chromatography showed that they contain a mixture of products, obtained apparently by the subsequent reaction of I with several molecules of the phosphorus ylide. Increasing the amount of ylide used forces the reaction towards the more substituted by-product. In the reaction of I with triphenylmethylenephosphorane it was possible to isolate the product substituted as completely as possible—2-isopropylidene-5-methylenequinuclidine (VI)—in preparative amounts.

The stereochemistry of the synthesis by the Wittig reaction of ethyl 5-methylene- and 5-ethylidenequinuclidine-2-carboxylates (IV and V) was studied with the help of NMR spectra. For comparison the spectra of 3-methylenequinuclidine (X), methyl 5-oxoquinuclidine-2-carboxylate (I) and 2-isopropylidene-5-methylenequinuclidine (VI) were recorded and a comparison was made also with the PMR spectra we reported previously for the geometric isomers of 3-ethylidenequinuclidine [6].

In the spectrum of 3-methylenequinuclidine four groups of signals belonging to the protons of the quinuclidine nucleus may be observed; the protons on C-4 and C-7* give strong signal of 4 pu (proton units) with δ 1.73 ppm; a quintet δ 3.42 ppm (1 pu) corresponding to the proton on C-3, an intense quartet of 4 pu with δ 2.82 ppm caused by protons at C-5 and C-6. At 3.50 ppm a peak, broadened by long-range spin-spin interactions, from the proton at C-1 is observed. The signals of the protons of the CH_2= group (8) appear at 4.69 and 4.80 ppm.

The same groups of signals may be seen in the spectrum of compound IV. However, the structure of each line in this case is noticeably more complex. Furthermore, two closely-spaced quartets of the methylene group (δ 4.15 and 4.17 ppm) and two triplets (1.26 and 1.27 ppm) of the methyl ester group may be observed. The presence of the two aggregates of lines corresponding to two ethyl groups may be explained by the fact that compound IV exists as a mixture of two diastereomers with relative amounts of 40 and 60%. As a confirmation of this thesis, there is a shift in the signals of the proton at C-3, which appear as the superposition of two poorly-resolved groups of peaks.

The spectrum of the keto ester I has an analogous character; for this, two peaks are observed (3.69 and 3.71 ppm), corresponding to the two methyls of the methoxycarbonyl groups of the two diastereomers of I.

The spectrum of compound V has a still more complicated structure and allows a clear-cut identification in the main only of the protons of the side chains: the CH_3 of the ethoxycarbonyl group (two triplets, the chemical shifts of which coincide in $CHCl_3$—δ 1.26 ppm—but are separated by 0.02 ppm in pyridine); the CH_2 of the ethoxycarbonyl group (δ 4.15 and 4.17 ppm); and the CH_3— (δ 1.59 ppm) and CH= (5.12 ppm) of the ethylidene group. Of signals belonging to the protons of the quinuclidine ring, in this case, one can find groups of lines centering at δ 2.30 ppm the integral intensity of which amounts to 0.25 to 0.3 pu. As has been shown earlier, [6] the geometric isomerism relative to the double bond of the 3-ethylidenequinuclidine shows up in the PMR spectrum as a marked difference in the chemical shifts of the proton at C-3. The proton at C-3 in the trans position to the substituent on the double bond is found to be in a stronger field than that in the cis position. A comparison of the PMR spectra of compound V with the geometric isomers of 3-ethylidenequinuclidine [6] shows that the signal observed in the spectrum of V at 2.30 ppm must be ascribed to the isomer with the trans orientation of the CH_3— at C-8 and the proton at C-3. The signal of the proton at C-3 of the other geometric isomer is in a weaker field and, in the case of V, is covered by the signals of other groups in the nucleus. Consequently, V is a mixture of geometric isomers analogous to the α and β isomers of 3-ethylidenequinuclidine [6]. However, in the present case, each of the geometric isomers of V may exist as two diastereomers.

On the basis of an examination of the PMR spectrum of V, it may be said that at least the trans form of this compound actually exists in the form of two pairs of diastereomers, since the signal at 2.30 ppm represents an aggretate of two groups of lines. Also favoring the theory of the existence of diastereomers, is the nature of the signal of the proton at the double bond, which is formed by the superposition of several groups of peaks. It may be supposed that, in connection with the distance of the double bond of the ethylidene group of V from the ethoxycarbonyl group, the chemical shifts of the methyl and methylene protons of the ester moieties in the two geometric isomers are practically identical and the corresponding differences in the chemical shifts are connected with the presence of diastereomeric forms.

In the PMR spectrum of compound VI the peak of the CH_3— group (δ 1.76 ppm) and the two CH_2= groups (signals in the interval from 4.57 to 4.92 ppm) may be distinctly seen. Of the protons of the quinuclidine nucleus, the most clear-cut signal is a quintet at δ 2.40 ppm, corresponding to the proton at C-3.

EXPERIMENTAL

Ethyl 5-oxoquinuclidine-2-carboxylate (II). 1 g (4.9 mmole) of 5-oxoquinuclidine-2-carboxylic acid hydrochloride was heated for three hours with 10 ml of a 10% alcoholic HCl acid solution. The reaction mass was then evaporated in a vacuum to dryness, and the cast traces of water and alcohol were removed by distillation twice with anhydrous benzene. The esterification with alcoholic HCl was repeated twice more. The material obtained after distilling off the alcohol was dissolved in 3 ml of water and treated with 50% potassium carbonate until alkaline to phenolphthalein. The base II that was liberated was extracted with ether, the extract was dried over potassium carbonate and evaporated in a vacuum, and the residue was distilled.

* Here and in what follows, in discussing the PMR spectra of quinuclidine derivatives, only the carbon atoms are numbered (see formula X in the equations) in the same way as in our previous publications [3, 6].

The yield of II with bp 107–108° (0.8 mm) was 0.65 g (84.4%). Colorless, mobile liquid, easily soluble in the usual organic solvents, less so in water n_D^{20} 1.4800. IR spectrum: 1740–1750 cm^{-1} (> C=O, $-COOC_2H_5$). Found, %: C 61.25; H 7.87; N 6.70. Calculated for $C_{10}H_{15}NO_3$, %: C 60.89; H 7.67; N 7.10.

Ethyl 5-methylenequinuclidine-2-carboxylate (IV). To a solution of sodium amide (from 1.25 g Na, 54 mmole) in 200 ml liquid ammonia was added 19.5 g (54 mmole) of triphenylmethylphosphonium bromide. The orange-red reaction mixture was diluted with 200 ml of anhydrous ether. The ammonia was evaporated, and with stirring a solution of 5 g (27 mmole) of methyl 5-oxoquinuclidine-2-carboxylate in 50 ml anhydrous ether was added. The reaction mixture became lighter and after 6 hours of boiling with stirring was pink. The inorganic salts and phosphorus compounds were filtered off and carefully extracted with 10% hydrochloric acid. The hydrochloric acid extract was boiled for 5 hours, and then repeatedly extracted with benzene. The ether and benzene solutions, containing nonbasic materials, were not subsequently studied further. The hydrochloric acid solution was evaporated under vacuum. The residue was made alkaline with a 50% K_2CO_3 solution and the "unsaponifiable" products of the reaction were extracted with ether. After removing the ether, 0.18 g of a mixture of products was obtained which GLC analysis showed to contain ~3% of 2-isopropenyl-5-methylenequinuclidine (VI, retention time 2.8 min) and about 96% of compounds having, apparently, the structure 2-acetyl-5-oxoquinuclidine and isomers of 2-acetyl-5-methylene- and 2-isopropenyl-5-oxoquinuclidine (retention times, 3.5, 4.8, and 5.5 min respectively).

The aqueous layer after extraction of the "unsaponifiable" reaction products was acidified with hydrochloric acid and evaporated to dryness. The residue was twice esterified by boiling with 20 ml of a 10% alcoholic solution of HCl for 3 hours with subsequent evaporation in a vacuum and dehydration of the reaction mixture by azeotropic distillation with benzene. The hydrochlorides of the ethyl esters II and IV that were formed as a result of the esterification were treated with a 50% K_2CO_3 solution and the bases liberated were extracted with ether. The ether extract, dried over sodium sulfate, was evaporated under a vacuum. The residue (2.91 g), according to GLC analysis, was a mixture of the bases IV and II (yields, respectively 13.5 and 40.6%, based on the keto ester I taken). The retention times were 6.2 and 9.4 min. Two vacuum fractionations gave the individual ester IV, bp 86–87° C (3 mm). Colorless liquid, readily soluble in the usual organic solvents, with difficulty in water, n_D^{20} 1.4895. IR spectrum: 1720–1740 cm^{-1} ($-COOC_2H_5$), 905, 1640, and 3090 cm^{-1} (=CH_2). Found, %: C 67.50; H 8.67; N 6.86. Calculated for $C_{11}H_{17}NO_2$, %: C 67.66; H 8.78; N 7.16. Hydrochloride was colorless crystals, mp 166–166.5° C (from acetone). The substance was readily soluble in water, alcohols and hot acetone, less so in hot ethyl acetate and in benzene. Found, %: C 57.07, 56.73; H 7.84, 7.90; N 6.11; Cl 15.50. Calculated for $C_{11}H_{17}NO_2 \cdot HCl$, %: C 57.01; H 7.83; N 6.05; Cl 15.30.

Ethyl 5-ethylidenequinuclidine-2-carboxylate (V) was obtained from 3.1 g (78 mmole) of sodium amide in liquid ammonia (250 ml) and 28.4 g (76 mmole) of triphenylmethylphosphonium bromide by a method similiar to IV. With V, the ester II was also formed (yields, according to GLC analysis 48.1% and 19.0%, retention times, 8.25 and 9.4 min, respectively). Careful fractionation of this mixture gave pure V, bp 124–125° C (5 mm). Colorless liquid, readily soluble in the usual organic solvents, sparingly soluble in water, n_D^{20} 1.4854, IR spectrum: 1730–1750 cm^{-1} ($-COOC_2H_5$), 1385 cm^{-1} (=CH–CH_3). Found, %: C 68.50; H 9.18; N 6.66. Calculated for $C_{12}H_{19}NO_2$, %: C 68.86; H 9.15; N 6.69.

2-Isopropenyl-2-methylenequinuclidine (VI). To a solution of sodium amide (from 4.32 g of sodium, 188 mmole) in 400 ml of liquid ammonia was added 67 g (188 mmole) of triphenylmethylphosphonium bromide. The orange-red reaction mixture was diluted with 400 ml of anhydrous ether. The ammonia was boiled off and then 11.47 g (62.5 mmole) of methyl 5-oxoquinuclidine-2-carboxylate (I) in 100 ml of anhydrous ether was added. After being boiled for 6 hours with stirring, the reaction mixture was worked up as described in the preceding experiments. From the "saponifiable part" was obtained 4.41 g of a mixture of the ethyl esters of 5-methylene- and 5-oxoquinuclidine-2-carboxylic acids. The yields of esters II and IV, from GLC analysis were 18.2 and 13.95% respectively. The "unsaponifiable" part consisted of 3.09 g of the same products as those formed in the synthesis of IV, but with a larger amount of compound VI (58.1%).

Distillation of this mixture gave a fraction with bp 84–90° (10 mm) enriched in VI. A solution of 0.65 g of this fraction in petroleum ether was placed on a column (58 × 1.8 cm) containing 50 g of alumina, moistened with petroleum ether. The mixture was eluted with a petroleum ether–ether mixture (9:1). The first 300 ml of eluate contained 0.5 g of pure compound VI with bp 86–87° (10 mm). Colorless, mobile liquid readily soluble in the common organic solvents, slightly in water, n_D^{20} 1.4965. Over-all yield of VI, 18.3%. IR spectrum: 980, 1640, 3080 and 3100 cm^{-1} (=CH_2). Found, %: C 80.60; H 10.64; N 8.67. Calculated for $C_{11}H_{17}N$, %: C 80.92; H 10.50; N 8.58.

3-Methylenequinuclidine (X). To a solution of sodium amide (from 1 g of sodium, 43.5 mmole) in 150 ml liquid ammonia was added 15.6 g (43.5 mmole) of triphenylmethylphosphonium bromide. The orange-red solution was diluted with 60 ml of anhydrous ether and, after the ammonia had been evaporated off, 2.7 g of 3-quinuclidone was added with stirring. The rapidly decolorizing reaction mixture was stirred at room temperature for 1 hour and then for 2 hours at the boil, the progress of the reaction being checked by paper-chromatography until the disappearance of the 3-quinuclidone spot, R_f 0.42. The precipitate was filtered off and washed with ether. The basic material was extracted from the ether with a solution of 10% hydrochloric acid. The hydrochloric acid solution was extracted with ether and chloroform, and was then made alkaline with a 50% solution of potassium carbonate and distilled with steam. The distillate (400 ml) was acidified with 1 N hydrochloric acid to a pH of 5 and evaporated under vacuum to dryness. The residue was treated with a 50% K_2CO_3 solution and extracted with ether. After the ether had been driven off, the residue was fractionated and gave 1.79 g (67.2%) of X with bp 59–61° (15 mm). Colorless, mobile liquid, readily soluble in water and the usual organic solvents, n_D^{20} 1.4930 [9], R_f 0.57 (an orange-pink spot). IR spectrum: 990, 1660, 3080 cm^{-1} (=CH_2). Found, %: C 77.60; H 10.30; N 11.06. Calculated for $C_8H_{13}N$, %: C 77.99; H 10.63; N 11.37. Hydrochloride, colorless crystals, mp 257–258° C. The substance was readily soluble in water, alcohol, and chloroform, soluble with difficulty in acetone, ethyl acetate, dioxane, and benzene, insoluble in ether. Found, %: C 60.23; H 8.88; Cl 22.22; N 8.65. Calculated for $C_8H_{13}N \cdot HCl$, %: C 60.17; H 8.83; Cl 22.21; N 8.77.

3-Formylquinuclidine (XI). To a suspension of 14.25 g (41.5 mmole) of methoxymethylenetriphenylphosphonium bromide in 100 ml of anhydrous ether was added 3.5 g (41.5 mmole) of phenyllithium in 70 ml of anhydrous ether over the period of an hour with stirring. The reaction mixture became dark red. Then a solution of 2.6 g of 3-quinuclidone in 50 ml anhydrous ether was added, some lightening of the reaction mixture and a change in the character of the precipitate being observed. Stirring was continued at room temperature for two hours, after which the mixture was boiled for about an hour, the progress of the reaction being checked by paper chromatography as in the previous experiment. The residue was separated off and repeatedly washed with ether. Diluted about 10 times, the ether solution was filtered from the additional precipitate and extracted three times with 10 ml of 18% hydrochloric acid. The combined acid extracts were washed with ether and treated with a 50% K_2CO_3 solution until alkaline to phenolphthalein. The product was extracted with warm chloroform and dried over K_2CO_3. After the solvent had been removed, the XI was distilled in vacuum. There was obtained 2.15 g (74.4%) of a volatile, mobile liquid with an ammoniacal odor, readily soluble in water, alcohols, and chloroform, bp 93–96° C (8 mm). IR spectrum: 1722, 2725, 2827 cm^{-1} (–CHO). R_f 0.64 (lilac-pink spot). Found, %: C 69.03, 69.46; H 9.37, 9.49; N 9.85. Calculated for $C_8H_{13}NO$, %: C 69.03; H 9.41; N 10.06.

The product readily picked up moisture from the air, changing to colorless crystals mp 49–52° during prolonged storage, and on heating the compound partially polymerized. Thiosemicarbazone had colorless crystals mp 184° C (decomp., from alcohol). Found, %: N 26.63; S 15.11. Calculated for $C_9H_{16}N_4S$, %: N 26.39; S 15.10.

The product and its semicarbazone were identical with the corresponding products of the reduction of ethyl quinuclidine-3-carboxylate with the calculated amount of sodium aluminum hydride [8].

Reaction of methyl 5-oxoquinuclidine-2-carboxylate with sodium acetylide. Pure dry acetylene was passed through a solution of sodium amide (from 0.61 g of Na, 26.5 mmole) in 100 ml liquid ammonia until the blue coloration disappeared. To the solution of sodium acetylide thus formed, was added with stirring 4.84 g (26.5 mmole) of methyl 5-oxoquinuclidine-2-carboxylate in 50 ml of anhydrous ether. The ammonia was removed and to the residue was added 30 ml of water and 25 ml of 50% sulfuric acid. After the solution had been made alkaline with K_2CO_3, 0.38 g (8.1%) of 5-oxoquinuclidine-2-carboxamide (III) was extracted with chloroform. Colorless crystals mp 130–131° C (from ethyl acetate). The product was soluble in water, alcohol, acetone, chloroform, benzene and dioxane, insoluble in ether and petroleum ether. IR spectrum: 1730 (>C=O), 3400, 3220, 1685 cm^{-1}(–$CONH_2$). Found, %: C 57.55; H 7.15; N 16.41. Calculated for $C_8H_{12}N_2O_2$, %: C 57.12; H 7.13; N 16.65.

Concentrated HCl was added to the aqueous solution obtained after the removal of the 5-oxoquinuclidine-2-carboxamide until it gave an acid reaction to Congo Red solution. The reaction mixture was evaporated to dryness under vacuum on a steam bath. The residue was boiled for 4 hours with 30 ml of a methanolic solution of HCl, and then the methanolic solution was separated from the solid matter and the procedure repeated twice more. The methanolic solutions were combined, separated from the precipitate of inorganic salts, and evaporated in vacuum. The residue was dissolved in 5 ml of water and treated with 50% K_2CO_3 solution to an alkaline reaction to phenolphthalein, and the base was extracted with ether, dried with K_2CO_3, and evaporated in vacuum. Fractionation yielded methyl 5-oxoquinuclidine-2-carboxylate (I), bp 115–120° C (0.3 mm), yield 1.57 g (32.4%), and methyl 5-hydroxy-5-ethylquinuclidine-2-carboxylate (VII), bp 130–132° C (0.3 mm), yield 0.87 g (15.8%). Colorless viscous liquid, easily soluble in water and the usual organic solvents, n_D^{20} 1.5120. IR spectrum 3200–3300 cm^{-1}(–OH), 2120 cm^{-1} (≡CH), 1750 cm^{-1}(–$COOCH_3$). Found, %: N 6.51; OH 8.46. Calculated for $C_{11}H_{15}NO_3$, %: N 6.79; OH 8.12.

5-Hydroxy-5-ethylquinuclidine-2-carboxylic hydrazine (VIII). 0.21 g (10 mmole) of the ester VII and 0.21 g (65 mmole) of hydrazine hydrate were boiled for 5 hours in 6 ml of anhydrous alcohol. The reaction mixture was evaporated under vacuum and the residue triturated with anhydrous ether. There was obtained 0.21 g (100%) of VIII. Colorless crystals, readily soluble in alcohol, slightly soluble in the other common organic solvents. Found, %: N 19.90, 19.81. Calculated for $C_{10}H_{15}N_3O_2$, %: N 20.08.

IR spectra were run on a UR-10 instrument; PMR spectra were recorded on an INM-4H-100 spectrometer (100 MH_Z); solvents used were chloroform and pyridine; internal standard of trimethylsilane.

GLC analysis was performed on a Carlo Erba Fractovap chromatograph. Column length 2 m, stationary phase was elastomer E-301, in a 20% concentration on Chromosorb W. Carrier gas was helium; rate of flow of gas was 10 *l*/hr; column temperature was 180° C.

Chromatography on paper ("for chromatography") was carried out by the descending method in the system: n-butanol—water—acetic acid (5:4:1). Detection with Dragendorff's reagent.

REFERENCES

1. L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, ZhOKh, 30, 519, 1960.

2. L. N. Yakhontov, L. I. Mastafanova, and M. V. Rubtsov, ZhOKh, 33, 3211, 1963.

3. L. N. Yakhontov, L. I. Mastafanova, S. L. Portnova, and M. V. Rubtsov, DAN, 162, 1075, 1962.

4. I. Ernest, Coll., 15, 322, 1950; G. R. Clemo and E. Hoggarth, J. Chem. Soc., 476, 1941.

5. M. V. Rubtsov, L. N. Yakhontov, and L. I. Mastafanova, Patent no. 175946, 1965; Byull. izobr. no. 21, 1965.

6. L. N. Yakhontov, L. I. Mastafanova, K. F. Turchin, Yu. N. Sheinker, and M. V. Rubtsov, DAN, 168, 118, 1966.

7. M. V. Rubtsov, L. N. Yakhontov, and L. I. Mastafanova, ZhOKh, 33, 1180, 1963.

8. L. I. Mastafanova, L. N. Yakhontov, and M. V. Rubtsov, KhGs [Chemistry of Heterocyclic Compounds], 858, 1965.

9. R. Lukeš and I. Ernest, Coll., 15, 150, 1950.

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