SYNTHESES IN THE QUINOLINE SERIES

III.* 2-FORMYL-8-HYDROXYQUINOLINE DERIVATIVES

I. A. Krasavin, Yu. P. Radin,
Yu. S. Ryabokobylko, B. V. Parusnikov,
and V. M. Dziomko

UDC 547.831.8:543.422.4:541.63

2-Formyl-8-hydroxyquinoline and 5,7-dimethyl-2-formyl-8-hydroxyquinoline derivatives were synthesized. The use of nitrophenols as the oxidizing agents in the reaction of the appropriate aminophenols with crotonaldehyde leads to a substantial increase in the yields of quinaldines. According to the IR spectroscopic data, the oximes of the formylhydroxyquinolines have a syn configuration.

2-Formyl-8-hydroxyquinoline (I) [2] and its oxime (II) [2-4], 2-quinolylhydrazone (III) [5, 6], 8-quinolylhydrazone (IV) [7, 8], and other derivatives [3, 9] are selective chelating agents and extractants for metal ions. The synthesis of aldehyde I is based on the oxidation of 8-benzyloxyquinaldine [10] or 8-acetoxyquinaldine (V) [2] with selenium dioxide and subsequent hydrolysis of the protective group, but both steps are complicated by side processes.

Sulfuric acid was found to be a reagent that makes it possible to selectively isolate the aldehyde from the mixture of oxidation products [11]. It forms the α-hydroxy(8-acetoxy-2-quinolyl)methanesulfonic acid inner salt (VII) with 8-acetoxy-2-formylquinoline (VI). The aldehyde carbonyl absorption at ∿1700 cm^{-1} is absent in the IR spectrum of VII, and there are intense bands of stretching vibrations of the SO_3^- anion at 1184 and 1251 cm^{-1}, of an ester carbonyl group at 1772 cm^{-1}, and of alcohol hydroxyl and NH^+ groups at ∿2850 and 3140 cm^{-1}.

Salt VII displays acid properties and is readily soluble in a cold dilute solution of sodium bicarbonate with CO_2 evolution. The addition of sodium hydroxide solution to the resulting solution gives a bright-red precipitate of sodium salt VIII, which acids convert to hydroxy aldehyde I. The corresponding derivatives (II-IV and IX) were obtained by reaction of I with hydroxylamine, 2- and 8-hydrazinoquinolines, and hydrazine hydrate.

2,5,7-Trimethyl-8-hydroxyquinoline (XI) was obtained from 4,6-dimethyl-2-aminophenol (X), 4,6-dimethyl-2-nitrophenol, and crotonaldehyde under the conditions of the Doebner–Miller reaction. The resinification that, as a rule, accompanies quinaldine syntheses is not observed in this case, and the yield of the product is unusually high – almost 1.4 moles per mole of starting amine (X). It is obvious that a considerable amount of amine X, formed during the Doebner–Miller reaction from the nitro compound, which acts as the oxidizing agent, also undergoes cyclization.

2,5,7-Trimethyl-8-hydroxyquinoline 1-oxide (XII) and 8-hydroxyquinaldine 1-oxide (XIII) were synthesized by oxidation of the corresponding bases (XI and XIV) with peracetic acid.

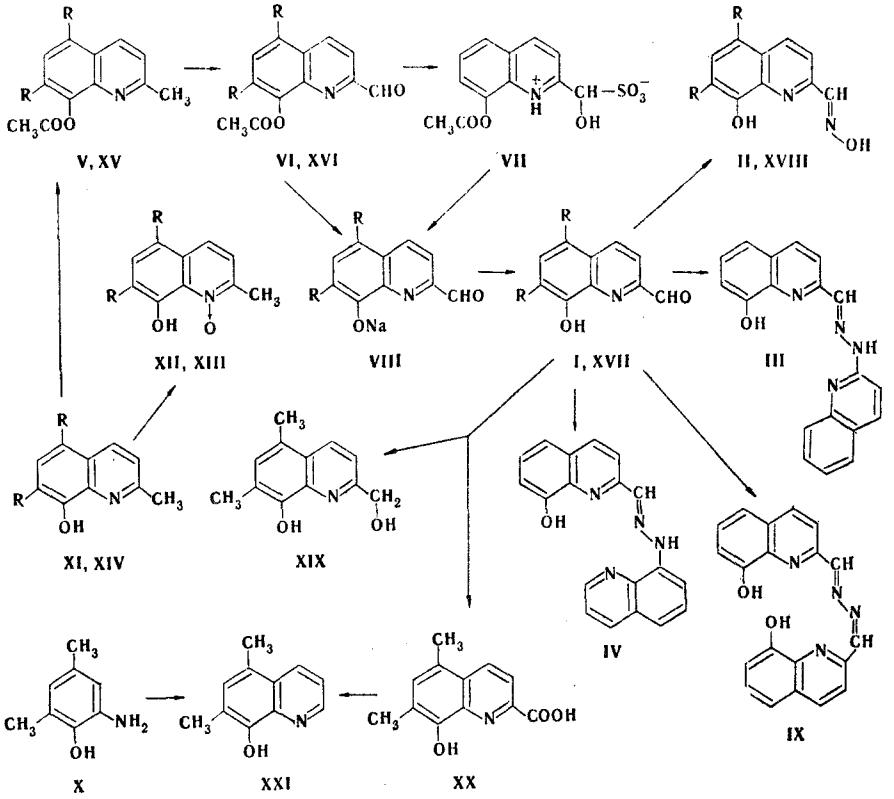
Acetylation of XI with acetic anhydride gave 2,5,7-trimethyl-8-acetoxyquinoline (XV), oxidation of which with selenium dioxide and subsequent alkaline hydrolysis of acetate XVI gave 5,7-dimethyl-2-formyl-8-hydroxyquinoline (XVII); oxime XVIII was obtained from the latter.

Of the two geometrical isomers of 2-formylquinoline oxime, only one is known; on the basis of a study of acylation and complexing reactions [12] and spectroscopic data [13] a syn configuration was assigned to it. Attempts to obtain the anti isomer of 2-formylquinoline oxime were unsuccessful [12].

*See [1] for communication II.

All-Union Scientific-Research Institute of Chemical Reagents and Ultrapure Chemical Substances, Moscow 107258. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 235-239, February, 1978. Original article submitted February 24, 1977.

 0009-3122/78/1402-0190$07.50 © 1978 Plenum Publishing Corporation



I, II, V, VI, VIII, XIII, XIV R = H; XI, XII, XV–XVIII R = CH_3

We also obtained only one form of 2-formyl-8-hydroxyquinoline oxime (II) and 5,7-dimethyl-2-formyl-8-hydroxyquinoline oxime (XVIII). The IR spectra of dilute solutions of these oximes in tetrachloroethylene contain two bands of OH stretching vibrations. The low frequency bands [ν_{OH} 3436 cm^{-1} ($\Delta\nu_{1/2}$ 42 cm^{-1}, ε 110 liter/mole·cm) and ν_{OH} 3429 cm^{-1} ($\Delta\nu_{1/2}$ 43 cm^{-1}, ε 111 liter/mole·cm), respectively] should be assigned to the stretching vibrations of the hydroxyl group in the 8 position of the molecule, since they are similar to the ν_{OH} bands in the spectra of 13 other 8-hydroxyquinoline derivatives that we investigated [ν_{OH} 3401-3459 cm^{-1} ($\Delta\nu_{1/2}$ 35-54 cm^{-1}, ε 70-137 liter/mole·cm)]. The high-frequency bands in the spectra of oxime II [ν_{OH} 3505 cm^{-1} ($\Delta\nu_{1/2}$ 22 cm^{-1}, ε 334 liter/mole·cm)] and oxime XVIII [ν_{OH} 3586 cm^{-1} ($\Delta\nu_{1/2}$ 22 cm^{-1}, ε 366 liter/mole·cm)], which differ markedly from them with respect to their width and intensity, belong to the OH stretching vibrations of the oxime group. The frequencies of these bands are close to the frequencies of the ν_{OH} bands of the free hydroxyl groups in the known syn isomers of 2-formylquinoline oxime (3593 cm^{-1}) [13] and 2-formylpyridine oxime (3580 cm^{-1} [14]; this makes it possible to assign a syn configuration to oximes II and XVIII. It is known that the strong intramolecular hydrogen bond included in a six-membered chelate ring in the anti isomers gives rise to an extremely large low-frequency shift of the band; for example, the ν_{OH} band in the spectrum of the anti isomer of 2-formylpyridine oxime is lowered to 2790 cm^{-1} [15].

In contrast to aldehyde I, which undergoes resinification under the conditions of the Cannizzaro reaction, its 5,7-dimethyl derivative (XVII) gives normal products of this reaction — (5,7-dimethyl-8-hydroxy-2-quinolyl)methanol (XIX) and 5,7-dimethyl-8-hydroxyquinoline-2-carboxylic acid (XX). Thermal decarboxylation of the latter gives 5,7-dimethyl-8-hydroxyquinoline (XXI), which we also obtained from 4,6-dimethyl-2-aminophenol under the conditions of the Skraup reaction.

In the IR spectrum of a dilute solution of dihydroxy derivative XIX in tetrachloroethylene the frequencies of the stretching vibrations of both the phenolic (3424 cm^{-1}) and alcohol (3468 cm^{-1} and shoulder at 3511 cm^{-1}) hydroxyl groups are lowered; this is probably explained by their simultaneous participation in an intramolecular hydrogen bond with the quinoline nitrogen atom.

EXPERIMENTAL

The IR spectra of tetrachloroethylene solutions (10^{-3} mole/liter) or KBr pellets of the compounds were recorded with a UR-10 spectrometer.

2-Formyl-8-hydroxyquinoline (I). A solution of 60.4 g (0.3 mole) of 8-acetoxyquinaldine (V) [10] in 150 ml of dioxane was added at 55-57°C to a suspension of 33.3 g (0.3 mole) of selenium dioxide in 375 ml of dry dioxane, and the mixture was stirred at 75-78° for 3 h. It was then treated with charcoal and filtered. Water (60 ml) was added to the filtrate, and the mixture was cooled with ice and saturated with sulfur dioxide. After 15 h, the precipitate was removed by suction filtration and mixed with 900 ml of water and 30 g of $NaHCO_3$. The solution was treated with charcoal and filtered, and 150 ml of 25% NaOH solution was added to the filtrate at 2°C. After 10 min, the red precipitate of sodium salt VIII was removed by suction filtration and mixed with 600 ml of water, 300 ml of chloroform, and 18 ml of acetic acid. The lower layer was dried and evaporated, and the residue was crystallized from 570 ml of n-heptane to give 28.2 g (54%) with mp 98.5-99°C (mp 98.5-99.5°C [10]). IR spectrum (KBr): $\nu_{C=O}$ 1707; ν_{OH} 3385 (inflection) and 3383 cm^{-1}.

α-Hydroxy(8-acetoxy-2-quinolyl)methanesulfonic Acid Inner Salt (VII). A stream of SO_2 was passed for 10 min through an ice-cooled solution of 2.15 g (0.01 mole) of 8-acetoxyl-1-formylquinoline (VI) [10] in 20 ml of dioxane and 2 ml of water. After 3 h, the precipitate was removed by suction filtration, washed with dioxane, and dried over NaOH to give 2.93 g (99%) of colorless crystals. IR spectrum (KBr): $\nu_{SO_3^-}$ 1184, 1251; $\nu_{C=O}$ (ester) 1772; ν_{NH^+} and ν_{OH} (alcohol) 2850, 3140 cm^{-1}. Found: C 48.6; H 4.0; N 4.9; S 11.3%. $C_{12}H_{11}NO_6S$. Calculated: C 48.5; H 3.7; N 4.7; S 10.8%.

Derivatives II-IV and IX were obtained from aldehyde I in refluxing ethanol.

2-Formyl-8-hydroxyquinoline Oxime (II). This compound was obtained in 81% yield as cream-colored crystals with mp 167.5-168°C (from ethanol). IR spectrum (KBr): ν_{N-O} 977; ν_{OH} 3362, 3413 cm^{-1}. Found: C 63.7; H 4.2; N 14.9%. $C_{10}H_8N_2O_2$. Calculated: 63.8; H 4.3; N 14.9%.

2-Formyl-8-hydroxyquinoline 2-Quinolylhydrazone (III). This compound was obtained in 98% yield as pale-yellow fibrous crystals with mp 265°C (dec., from dioxane). Found: C 72.4; H 4.7; N 17.8%. $C_{19}H_{14}N_4O$. Calculated: C 72.6; H 4.5; N 17.8%.

2-Formyl-8-hydroxyquinoline 8-Quinolylhydrazone (IV). This compound was obtained in 97.5% yield as bright-yellow fibrous needles (from benzene) with mp 201.5-202°C; on further heating the melt solidified and remelted at 223-223.5°C. Found: C 72.9; H 4.6; N 17.7%. $C_{19}H_{14}N_4O$. Calculated: C 72.6; H 4.5; N 17.8%.

8-Hydroxyquinaldazine (IX). This compound was obtained in 95% yield as bright-yellow plates with mp 261°C (dec., from dioxane). IR spectrum (KBr): ν_{OH} 3450 cm^{-1}. Found: C 70.4; H 4.5; N 16.1%. $C_{20}H_{14}N_4O_2$. Calculated: C 70.2; H 4.1; N 16.4%.

2,5,7-Trimethyl-8-hydroxyquinoline (XI). A 42-g (0.6 mole) sample of crotonaldehyde was added at 100°C in the course of 45 min to a mixture of 41.2 g (0.3 mole) of 4,6-dimethyl-2-aminophenol (X), 150 ml of concentrated HCl, and 25.0 g (0.15 mole) of 4,6-dimethyl-2-nitrophenol, and the mixture was stirred at 100°C for another 5 h. The excess nitro compound was removed by steam distillation, and the residue was diluted with water to volume of 1.2 liter, refluxed with charcoal, and filtered hot. It was then cooled and filtered to give 85.7 g of the hydrochloride of XI; additional amount of product was isolated from the filtrate for a total yield of 93.2 g, which amounts to 1.39 mole per mole of the starting amine X or 92.6% based on the sum of the amino and nitro compounds. The hydrochloride was obtained as bright-yellow needles (from 10% HCl) and was converted quantitatively to base XI, with bp 136-140°C (4 mm) [colorless needles with mp 84.5-85.5°C (from ethanol)], by neutralization and extraction with benzene. IR spectrum (KBr): ν_{OH} ~ 3260 cm^{-1}. Found: C 77.2; H 7.0; N 7.2%. $C_{12}H_{13}NO$. Calculated: C 77.0; H 7.0; N 7.5%.

2,5,7-Trimethyl-8-hydroxyquinoline 1-Oxide (XII). A 13.6-g (0.12 mole) sample of 30% H_2O_2 was mixed with 10.5 g (0.1 mole) of acetic anhydride, and the mixture was added after 2 days to a solution of 5.6 g (0.03 mole) of XI in 30 ml of chloroform. The mixture was stirred for 15 h, after which it was extracted with chloroform. The extract was dried over Na_2CO_3 and worked up to give 3.73 g (61%) of oxide XII as bright-yellow fine needles with mp 126-126.5°C (from ethanol). IR spectrum (KBr): ν_{N-O} 1270 cm^{-1}. Found: C 70.7; H 6.6;

N 6.9%. $C_{12}H_{13}NO_2$. Calculated: C 70.9; H 6.4; N 6.9%.

2-Formyl-8-hydroxyquinoline 1-Oxide (XIII). This compound was obtained in 30% yield as yellow needles with mp 103.5-104°C (from water). IR spectrum (KBr): ν_{N-O} 1285 cm^{-1}. Found: C 68.8; H 5.6; N 8.0%. $C_{10}H_9NO_2$. Calculated: C 68.6; H 5.2; N 8.0%.

2,5,7-Trimethyl-8-acetoxyquinoline (XV). A solution of 56.2 g (0.3 mole) of base XI in 240 ml of acetic anhydride was refluxed, after which it was vacuum distilled. The fraction with bp 165-167°C (4 mm) was collected to give 63.5 g (92%) of yellow crystals with mp 64-65°C (from petroleum ether with cooling to −20°C); the product is hydrolyzed by air moisture. Found: C 73.2; H 6.6; N 6.3%. $C_{14}H_{15}NO_2$. Calculated: C 73.3; H 6.6; N 6.1%.

5,7-Dimethyl-2-formyl-8-hydroxyquinoline (XVII). A solution of 11.5 g (0.05 mole) of acetoxy derivative XV in 50 ml of dioxane was added in the course of 2 h to a heated (to 50°C) suspension of 5.66 g (0.051 mole) of selenium dioxide in 150 ml of dry dioxane, after which the mixture was stirred at 75-80°C for 3 h. It was then treated with charcoal and filtered, and the filtrate was vacuum evaporated at 45-50°C. The residue was dissolved in 100 ml of toluene, and 560 ml of 5% KOH was added with vigorous stirring at 0°C. The alkaline layer was separated rapidly and neutralized to pH 7 to give 8.1 g (80%) of crude aldehyde XVII. For purification, a solution of the product in acetone was allowed to stand in an evaporating dish until evaporation was complete, and the fluffy crystals were separated from the crust of the more contaminated substance; crystallization from cyclohexane gave gold-yellow needles with mp 115.5-116°C. IR spectrum (KBr): $\nu_{C=O}$ 1705 and ν_{OH} 3401 cm^{-1}. Found: C 71.5; H 5.2; N 6.7%. $C_{12}H_{11}NO_2$. Calculated: C 71.6; H 5.5; N 7.0%.

5,7-Dimethyl-2-formyl-8-hydroxyquinoline Oxime (XVIII). This compound was obtained in 97% yield as yellow needles with mp 204-204.5°C (from ethanol). IR spectrum (KBr): ν_{N-O} 970 and ν_{OH} 3190 and 3374 cm^{-1}. Found: C 66.6; H 5.9; N 13.1%. $C_{12}H_{12}N_2O_2$. Calculated: C 66.7; H 5.6; N 13.0%.

(5,7-Dimethyl-8-hydroxy-2-quinolyl)methanol (XIX) and 5,7-Dimethyl-8-hydroxyquinoline-2-carboxylic Acid (XX). A solution of 14 g of KOH in 100 ml of ethanol was added to a solution of 5.03 g (0.025 mole) of aldehyde XVII in 100 ml of hot ethanol, and the mixture was refluxed for 10 min. The ethanol was then removed in vacuo, and the residue was dissolved in 300 ml of water. A stream of CO_2 was bubbled into the solution, and the precipitate was removed by filtration, dried, and extracted with boiling n-heptane. Workup of the extract gave 1.29 g (50.8%) of dihydroxy derivative XIX with mp 135.5-136°C (from n-heptane). IR spectrum (KBr): ν_{C-O} 1054, ν_{OH} 3351 (8-OH), and 3399 cm^{-1} (alcohol). Found: C 71.1; H 6.7; N 6.7%. $C_{12}H_{13}NO_2$. Calculated: C 70.9; H 6.4; N 6.9%.

The filtrate from the separation of the precipitated XIX was acidified to pH 3 with hydrochloric acid to give 1.94 g (71.5%) of acid XX as short yellow needles with mp 238°C (dec., from 50% dioxane). IR spectrum (KBr): $\nu_{C=O}$ 1725, ν_{OH} 3203 (COOH), and 3348 cm^{-1} (8-OH). Found: C 66.5; H 5.1; N 6.4%. $C_{12}H_{11}NO_3$. Calculated: C 66.4; H 5.1; N 6.4%.

5,7-Dimethyl-8-hydroxyquinoline (XXI). A) 13.72-g (0.1 mole) sample of 4,6-dimethyl-2-aminophenol (X), 8.36 g (0.05 mole) of 4,6-dimethyl-2-nitrophenol, and 37 g (0.4 mole) of glycerol were mixed in a flask with an efficient reflux condenser, 32 g of oleum (4% free SO_3) was added, and the mixture was heated carefully until an exothermic reaction commenced. When the exothermic reaction subsided, the mixture was refluxed for another 3 h and diluted with water. The nitro compound was removed by steam distillation, the residue was made alkaline to pH 9, and the product was removed by steam distillation to give 14.55 g (84%) of a product with bp 126-129°C (4 mm) [colorless crystals with mp 96-96.5°C (from ethanol)]. IR spectrum (tetrachloroethylene): ν_{OH} 3412 cm^{-1}. Found: C 76.3; H 6.6; N 8.1%. $C_{11}H_{11}NO$. Calculated: C 76.3; H 6.4; N 8.1%.

B) A 0.18-g (0.0008 mole) sample of acid XX was heated at 240-250°C for 15 min, after which base XXI was removed by steam distillation to give 0.10 g (70%) of a product with mp 95.5-96°C (from ethanol); no melting-point depression was observed for a mixture of this product with a sample obtained by method A.

LITERATURE CITED

1. V. M. Dziomko and I. A. Krasavin, Khim. Geterotsikl. Soedin., No. 1, 281 (1967).
2. V. M. Dziomko and I. A. Krasavin, Trudy IREA, No. 26, 29 (1964).
3. J. Reihsig and H. W. Krause, J. Prakt. Chem., 31, 167 (1966).

4. R. L. Stevenson and H. Freiser, Anal. Chem., 39, 1354 (1967).
5. V. M. Dziomko, I. A. Krasavin, and I. N. Kremenskaya, Summaries of Papers Presented at the Twentieth International Congress on Theoretical and Applied Chemistry [in Russian] Moscow (1965), Section E, p. 64.
6. T. Rudolph and J. P. Phillips, Anal. Chim. Acta, 34, 235 (1966).
7. E. A. Bozhevol'nov, V. M. Dziomko, L. F. Fedorova, and I. A. Krasavin, USSR Author's Certificate No. 210458 (1966); Byull. Izobr., No. 6, 94 (1968).
8. E. A. Bozhevol'nov, L. F. Fedorova, I. A. Krasavin, and V. M. Dziomko, Zh. Anal. Khim., 24, 531 (1969).
9. E. Suenaga, Nippon Kagaku Zasshi, 82, 1059 (1961).
10. J. Büchi, A. Aebi, A. Deflorin, and H. Hurni, Helv. Chim. Acta, 36, 1676 (1956).
11. I. A. Krasavin, B. V. Parusnikov, Yu. P. Radin, and V. M. Dziomko, USSR Author's Certificate No. 514804 (1974); Byull. Izobr., No. 19, 52 (1976).
12. T. W. J. Taylor, D. H. G. Winckles, and M. S. Marks, J. Chem. Soc., 2778 (1931).
13. S. F. Mason, J. Chem. Soc., 22 (1960).
14. D. Hadži and L. Premru, Spectrochim. Acta, 23A, 35 (1967).
15. E. J. Poziomek and L. G. Vaughan, J. Pharm. Sci., 58, 811 (1965).

STEREOCHEMISTRY OF THE ASYMMETRIC REDUCTION OF N-(α-PHENYLETHYL)-$\Delta^{8,9}$-HEXAHYDRO-4-PYRINDONE*

G. V. Grishina, V. M. Potapov, and T. A. Liberchuk

UDC 541.632:547.834:542.942

The reduction of optically active N-(α-phenylethyl)-$\Delta^{8,9}$-hexahydro-4-pyrindone with lithium aluminum hydride proceeds as asymmetric stereospecific 1,4-hydride addition and leads to the formation of primarily the thermodynamically stable trans-(8S,9S)-N-(α-phenylethyl)octahydro-4-pyrindone and a small amount of the corresponding cis isomer. Only cis-(8S,9S)-octahydro-4-pyrindone was obtained from each isomer and the mixture of isomers after removal of the chiral substituent from the nitrogen atom. The absolute configurations of the compounds obtained were established on the basis of circular dichroism data and the octant rule.

Continuing our study of methods for the synthesis of chiral γ-piperidones and their conformational behavior we investigated the stereochemical specificity of the reduction of optically active N-(α-phenylethyl)-$\Delta^{8,9}$-hexahydro-4-pyrindone (I) with lithium aluminum hydride.

The reduction of chiral enamino ketone I with lithium aluminum hydride and the isolation of the reaction products were accomplished as in [2] with equimolar ratios of the reagents. Column chromatography of the reaction mixture on aluminum oxide and silica gel gave N-(α-phenylethyl)octahydro-4-pyrindone (II) and N-(α-phenylethyl)octahydro-4-pyrindole (III) in quantitative yield in a ratio of 3:1; the structures and compositions of the products were confirmed by the result of elementary analysis, mass spectrometry, and IR and PMR spectroscopy (see the scheme on the following page).

Chromatography of the analytically pure octahydro-4-pyrindone II after separation with a column in various systems of solvents on Silufol showed the presence of a mixture of two isomers, IIa and IIb, with considerable predominance of isomer IIa. Only traces of isomer IIb were detected by chromatographic monitoring of the reaction mixture during and after reduction. The amount of isomer IIb increased somewhat on contact with the sorbent. Chromatographically individual isomer IIa was isolated from the mixture of isomers by means of column chromatography on silica gel; we were able to obtain isomer IIb in small amounts after repeated column chromatography of isomer IIb-enriched fractions. On the basis of the results of chromatographic separation of the mixture of isomers IIa and IIb it was established that the isomer ratio is 8:1.

*Communication XLVIII from "Stereochemical Studies." See [1] for communication XLVII.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 240-245, February, 1978. Original article submitted April 6, 1977.

 0009-3122/78/1402-0194$07.50 © 1978 Plenum Publishing Corporation