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SYNTHESIS OF CYCLIC IODONIUM SALTS CONTAINING AN ASYMMETRIC CARBON ATOM

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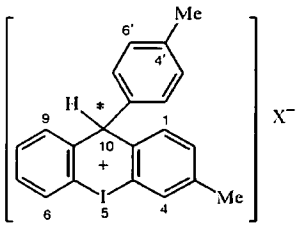
We report the synthesis of two iodonium salts with an asymmetric carbon atom in the cation, viz. 3-methyl-10H,10-(4-tolyl)dibenz[b,e]iodinium tetrafluoroborate and the salt of the same cation with the anion of (-)-mono(N-α-phenylethyl)maleic acid amide as well as the synthesis of 3-methyl-10H-dibenz[b,e]-iodinium tetrafluoroborate.

The chemistry of iodonium salts has been developed successfully over a long time but particularly intensively in recent years [1-4]. These compounds serve as convenient objects for studying the mechanisms of nucleophilic and radical substitution in the aromatic series in order to establish the regularities of the influence of electronic and steric factors on the reactions. Iodonium salts are also used as arylating agents. However, in spite of the wide research on this class of compounds, optically active iodonium salts have not been described until now even though chiral compounds are mentioned in a series of synthesized iodonium salts (see, e.g. [4]). In addition, such salts should be not just of theoretical interest. Diaryliodonium salts, including those with organic acid anions, are stable materials, readily crystallized, having quite high melting points, and able to serve as resolving reagents for racemates of optically active anions.

In our work we report the synthesis of two previously unknown iodonium salts containing an asymmetric carbon atom in the cation, i.e. 3-methyl-10H,10-(*p*-tolyl)dibenz[b,e]iodinium tetrafluoroborate (I) and salts of the same cation with the optically active anion of (-)-mono(N-α-phenylethyl)maleic acid amide (II).



I, II

I X = BF_4^-, II X = (−)PhCH(Me)NHCO–CH=CH–COO (*)

The precursor of salts I and II, *o*-iodophenyldi(*p*-tolyl)methane (III), was prepared by us according to Scheme 1.

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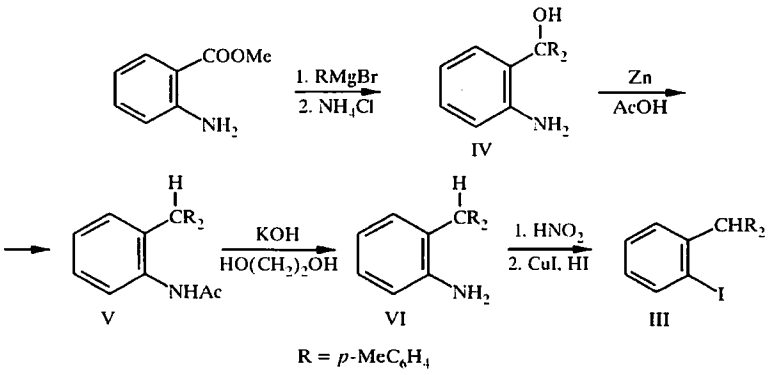
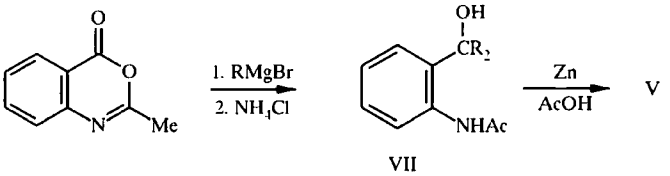
Scheme 1



In the first stage, methyl anthranilate and *p*-tolylmagnesium bromide in the usual conditions gave a 66% yield of *o*-aminophenyldi(*p*-tolyl)carbinol (IV), reduction of which with zinc in acetic acid gave a quantitative yield of *o*-acetamidophenyldi(*p*-tolyl)methane (V). Basic hydrolysis of the latter gave *o*-aminophenyldi-(*p*-tolyl)methane (VI), diazotization of which then gave *o*-iodophenyldi(*p*-tolyl)methane (III). The intermediate compound V in the above synthesis was also obtained by an alternative route via the action of *p*-tolylmagnesium bromide on 2-methylbenz-3,1-oxazin-4-one ("acetylanthranil") and subsequent reduction of the *o*-acetaminophenyldi(*p*-tolyl)carbinol (VII) formed (Scheme 2).

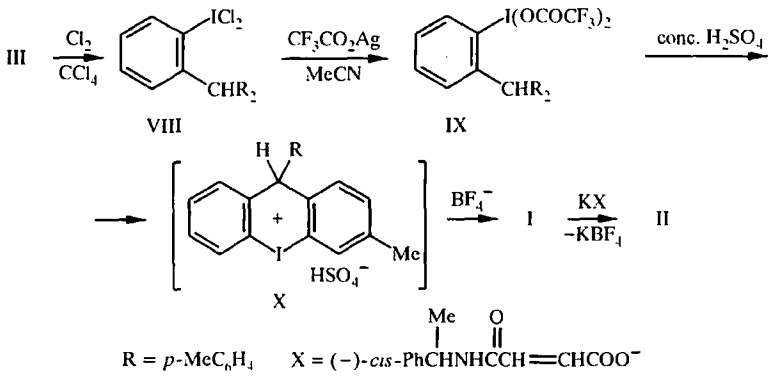
Scheme 2



It should be noted that introduction of iodine into one of the earlier stages of the synthesis was unsuccessful since an iodine atom in *ortho* position relative to the reaction center apparently causes significant steric hindrance to the reaction of *p*-tolylmagnesium bromide with methyl *o*-iodobenzoate or with *o*-iodo-*p'*-methylbenzophenone. This type of example has been reported in the literature (see, e.g. [5]). We were also unable to diazotize the amino group in carbinol IV since the latter, in the presence of strong mineral acids, is readily cyclized to 3-methyl-9-(*p*-tolyl)acridine which was identified by us via mass spectrometry, *m/z*: 283 $[M]^+$, 268 $[M-15]^+$, 142.5 $[M]^{++}$.

Exchange of the amino group for iodine in *o*-aminophenyldi(*p*-tolyl)methane (IV) could be brought about in 65% yield but only by the method [6] *via* diazotization of the sulfate of this amine in (1:3) mixture of 20% sulfuric and glacial acetic acid (since both the amine sulfate and the corresponding diazonium sulfate are very poorly soluble in water). Subsequently, the diazonium salt was decomposed in a two-phase system of CuI solution in concentrated HI mixed with an equal volume of ether. The obtained *o*-iodophenyldi(*p*-tolyl)methane III is a colorless crystalline material with mp 92-93°C, readily soluble in benzene, ether, $CHCl_3$, and CCl_4, extremely difficultly soluble in acetic acid and acetic anhydride, and insoluble in water and concentrated sulfuric acid. On account of the indicated above poor solubility of iodotriarylmethane III in acetic anhydride and in sulfuric acid, it appears not to be oxidized to the corresponding iodoso derivative (the immediate precursor of salt I) by peracetic and persulfuric acids which are the commonly used oxidizing agents in similar cases. We were only able to oxidize the iodine atom in compound III using chlorine (Scheme 3).

Scheme 3



To prepare the salt I dichloride of *o*-iodosophenyldi(*p*-tolyl)methane (VIII) produced was treated with silver trifluoroacetate according to method [7] to the more stable iodosobistrifluoroacetate IX, cyclization of which was carried out with concentrated sulfuric acid as described in [8] and this occurs almost instantly to give 3-methyl-10H,10-(*p*-tolyl)dibenz[b,e]iodinium bisulfate (X). Addition of NH_4BF_4 to a solution of the latter precipitated the salt I in 66% yield (based on iodide III, Scheme 3).

The PMR spectrum of salt shows singlets for the protons of the two methyl groups at 2.26 and 2.50, the methine proton at 6.15, a symmetrical multiplet for the *p*-tolyl aromatic signals at 6.75-7.18, and a multiplet for the aromatic protons of the two benzene rings annelated to the central ring at 7.50-8.35 ppm. The integrated areas for these groups of signals are 3:3:1:4:7 respectively.

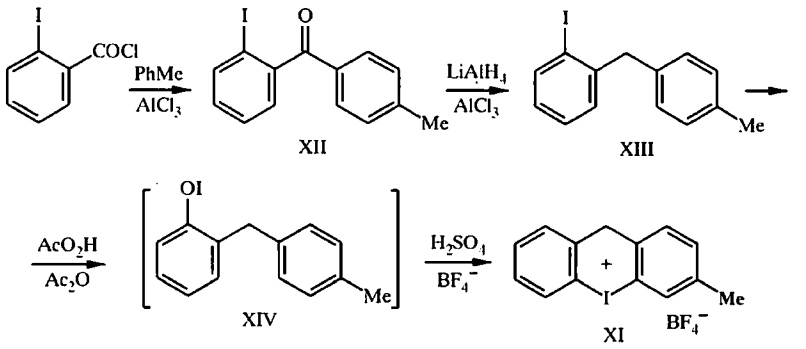
In order to detect the asymmetric carbon atom in cation of salt I using PMR spectroscopy, the salt treated with an alcoholic solution of mixture of equal amounts of (-)-mono(N-α-phenylethyl)maleic acid amide and KOH to give salt II containing the optically active anion. The PMR spectrum of a solution of salt II in DMSO-d_6 showed clear doubling of the signals for 1-, 4-, and 6-H in the cation and also the α-vinyl and methine protons in the anion. The spectrum of solution of the same salt in CD_2Cl_2 also showed doubling of the signal for the 3-CH_3 in the cation. This proves that the salt II exists on the PMR time scale as a mixture of diastereomeric ion pairs.

In conclusion, it should be noted that we have also synthesized the analog of salt I unsubstituted at the bridge, i.e. 3-methyl-10H-dibenz[b,e]iodinium tetrafluoroborate (XI) according Scheme 4:

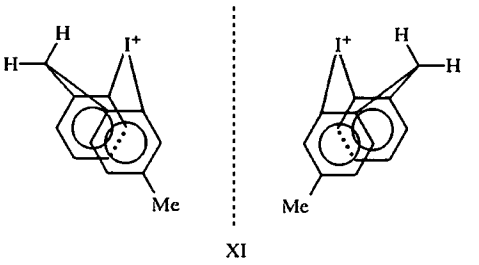
TABLE 1. Characteristics for Newly Synthesized Compounds.

Compound	Empirical formula	Found, % / Calculated, %			IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N or I		
I	$C_{21}H_{18}BF_4I$	52.16 / 52.10	3.83 / 3.75			66
III	$C_{21}H_{19}I$	62.98 / 63.33	4.69 / 4.81	32.23 / 31.86		61
IV	$C_{21}H_{21}NO$	82.89 / 83.13	7.11 / 6.98	4.42 / 4.61	3600-3100 (OH), 3500 3400 (NH_2), 1600 (arom.)	66
V	$C_{23}H_{23}NO$	83.32 / 83.85	7.09 / 7.04	4.28 / 4.25	3360-3280 (NH) 1660 (CO "amide I") 1460 ("amide II")	~100 (A) 94 (B)
VII	$C_{23}H_{23}NO_2$	79.95 / 79.97	6.77 / 6.71	4.01 / 4.06	3580 (OH), 3385 (NH) 1670 (CO "amide I") 1460 ("amide II") 1530 (arom.) (in CH_2Cl_2)	71
XI	$C_{14}H_{12}BF_4I$	42.48 / 42.68	3.01 / 3.07			83
XII	$C_{14}H_{11}IO$	52.31 / 52.20	3.62 / 3.44	39.67 / 39.40		45
XIII	$C_{14}H_{13}I$	54.33 / 54.57	4.36 / 4.25			72

Scheme 4



Although the cation of salt XI does not contain an asymmetric carbon atom, on account of the nonplanar structure of such iodonium cations [9], the compound in the crystalline state must also possess molecular asymmetry but this is apparently not retained in solution thanks to the mobility of the central heterocycle.



EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer for suspensions in vaseline oil and in CH_2Cl_2 solution. PMR spectra were measured on a Varian XL-400 instrument with CD_2Cl_2 and DMSO-d_6 solvents. Mass spectra were obtained on a Kratos MS-25-RFA instrument (25 m × 0.32 mm capillary column, liquid phase CP-Sil 8CB, helium carrier gas). The ionization intensity was 50 eV and the source temperature 250°C.

Parameters for the compounds synthesized for the first time are given in Table 1.

2-Methylbenz-3,1-oxazin-4-one was synthesized by a known method [10]; mp 79°C, bp 143°C/11 mm Hg.

o-Aminophenyldi(*p*-tolyl)carbinol (IV). Solution of methyl anthranilate (17.4 g, 0.12 mol) in absolute ether (50 ml) was added dropwise at 0°C to solution of *p*-tolylmagnesium bromide which had been prepared from magnesium (12 g, 0.5 mol) and *p*-bromotoluene (80 g, 0.47 mol) in absolute ether (350 ml). The mixture obtained was refluxed for 1 h and held at room temperature for about 16 h. The formed dimagnesium derivative of the aminocarbinol was precipitated by addition of petroleum ether. The supernatant liquid which contained the by-product *p,p'*-ditolyl was separated, transferring to another flask with argon, and the precipitate was washed with a mixture of ether and petroleum ether (1: 1), after which the liquid phase was also transferred with argon. The precipitate was then treated with ether (50 ml) and excess of concentrated aqueous ammonium chloride solution until the precipitate dissolved. The organic layer of the reaction mixture was separated, combined with chloroform extracts of the aqueous layer, washed with water, dried, and the solvent distilled off to give product IV (24 g); mp 69.0-69.5°C (alcohol).

***o*-Acetaminophenyldi(*p*-tolyl)carbinol (VII).** Solution of 2-methylbenz-3,1-oxazin-4-one (20 g, 0.124 mol) in absolute ether (90 ml) was added dropwise with stirring at 0°C to solution of *p*-tolylmagnesium bromide prepared from magnesium (9.1 g, 0.37 mol) and 4-bromotoluene (63 g, 0.37 mol) in absolute ether (300 ml).

The reaction mixture was held at room temperature for 1 day and then ether (250 ml) was distilled off. Petroleum ether (500 ml) was added to the residue which was then stirred, the liquid phase decanted, and ether (100 ml) and solution of NH_4Cl (100 g) in water (300 ml) were added to the residue. The precipitated product was filtered off, washed with water, and dried to give compound VII (30.5 g, 71%); mp 208-209°C (alcohol).

***o*-Acetaminophenyldi(*p*-tolyl)methane (V).** A. Powdered zinc (about 6 g) was added in small portions to the light brown solution of aminocarbinol IV (9.31 g, 30.1 mmol) in glacial acetic acid (153 ml) and water (100 ml) until the solution became colorless. The product V was precipitated with water, washed with water, and thoroughly dried in vacuo. Yield 10.16 g (quantitative); mp 169.5-170.5°C (glacial acetic acid).

B. Powdered zinc (13 g) was added in portions to solution of acetaminocarbinol VII (20 g, 58 mmol) in AcOH (200 ml) and water (120 ml) at 100°C over 2 h. Product V (17.9 g) was obtained; mp 169-170°C. A mixed sample with that obtained by method A did not give a depression of melting point.

***o*-Iodophenyldi(*p*-tolyl)methane (III).** Solution of compound V (22.44 g, 0.07 mol) and KOH (8 g, 0.14 mol) in ethylene glycol (400 ml) was refluxed for 10 h (monitored by TLC). The reaction mixture was then cooled, poured onto ice, extracted with benzene, and the extract thoroughly washed with water and dried with K_2CO_3. Benzene was distilled off to give *o*-aminophenyldi(*p*-tolyl)methane (VI, 17.22 g) which was converted to sulfate using H_2SO_4 (20%, 60 ml) without any further purification. To amine sulfate obtained about 10 ml of 20% H_2SO_4 and acetic acid (about 200 ml) were further added until the salt dissolved completely and then the diluted solution of $NaNO_2$ (5.0 g, 0.07 mol) was added. The clear diazo solution was gradually added to previously prepared solution of mixture of CuI (22.04 g, 0.12 mol), KI (15 g, 0.09 mol), concentrated HI (150 ml), and ether (150 ml). At the completion of the reaction the CuI precipitate was filtered off and washed with ether and the aqueous layer of the filtrate was extracted with ether. The combined organic layers, ether from the CuI wash, and the ether extracts were decolorized by washing with $NaHSO_3$ solution and water and dried using $MgSO_4$. After distillation of ether the residue was crystallized from alcohol to give product III (15.53 g, 61% based on the triarylmethane V); mp 92-93°C.

3-Methyl-10H,10-(*p*-tolyl)dibenz[b,e]iodinium Tetrafluoroborate (I). Through saturated solution of iodoarene III (5.2 g, 13 mmol) in CCl_4 protected from the light a stream of dry chlorine was passed at 5-10°C until bright yellow precipitate of *o*-iodosophenyldi(*p*-tolyl)methane (VIII) was produced. Petroleum ether (4-5 ml) was added to the reaction mixture and chlorine was again passed until precipitation was complete. The VIII dichloride precipitate was washed with CCl_4 and then pentane and dried in air to give a yield of 6.1 g (quantitative). The obtained iodosodichloride VIII (6.1 g, 13mmol) in dry acetonitrile (40 ml) was then treated, under stirring, with solution of silver trifluoroacetate (5.75 g, 26 mmol) in dry acetonitrile (50 ml) [11]. The precipitated AgCl was filtered off, acetonitrile evaporated in vacuo, and the oily residue dissolved in a minimum amount of absolute ether. Petroleum ether was added to the clear solution obtained to precipitate *o*-iodosophenyldi(*p*-tolyl)methane bistrifluoroacetate (IX, 5.93 g, 73%). A previously prepared mixture of acetic anhydride (5 ml) and concentrated H_2SO_4 (1 ml) was added dropwise with stirring at 0°C to solution of bistrifluoroacetate IX (5.9 g, 9.5 mmol) in acetic anhydride (32 ml) and acetic acid (45 ml). After 5 min, a sample of the reaction mixture gave a negative oxidant (KI + starch solution) test. The dark mass obtained containing the salt X was added to a solution of NH_4BF_4 (10 g, 95 mmol) in water (100 ml). The precipitated colorless product I was filtered and washed with ether. The aqueous filtrate was extracted with mixture of nitromethane and chloroform (3:1 by volume), evaporated to volume of 1-2 ml, and then precipitated by addition of petroleum ether to recover an additional amount of salt I. The overall yield of product I was 4.17 g (66%, based on iodoarene III). For purification, it was dissolved in CH_2Cl_2 and the solution filtered through a thin layer (7-10 mm, d = 15 mm) of alumina. The filtrate was evaporated in vacuo almost to dryness and the salt I was precipitated by addition of pentane, filtered off, recrystallized from alcohol, and again precipitated from CH_2Cl_2 solution using pentane; mp 242-243°C (with decomposition).

3-Methyl-10-(*p*-tolyl)-10H-dibenz[b,e]iodinium (-)-N-(α-phenylethyl)maleamate (II). Mixture of (-)-mono(N-α-phenylethyl)maleic acid amide (0.0497 g, 2.27×10^{-4} mol) and KOH (0.0127 g, 2.27×10^{-4} mol) in ethanol (9 ml) was added to solution of salt I (0.1099 g, 2.27×10^{-4} mol) in ethanol (13 ml). The precipitated KBF_4 was filtered off, the filtrate evaporated to dryness in vacuo, and the residue of product II was dried in vacuo over P_2O_5. PMR spectrum of the cation of salt II (DMSO-d_6): 8.18 and 8.15 (1H, two d, J = 8 Hz, 6-H); 7.99 and 7.96

(1H, two s, 4-H); 7.93 (1H, d, J = 7 Hz, 9-H); 7.82 and 7.81 (1H, two d, 1-H); 7.65 (1H, t, J = 8 Hz, 7-H): 7.47 (1H, d, J = 7 Hz, 2-H); 7.43 (1H, br. t, J = 8 Hz, 8-H); 7.0 and 6.66 (4H, AA'BB' system, 2'-, 6'- and 3'-, 5'-H); 2.36 and 2.34 (3H, two s, 3-CH_3); 2.15 ppm (3H, s, 4'-CH_3). PMR spectrum of the anion of salt II: 11.2 (1H, br. s, NH); 7.3-7.2 (5H, m, C_6H_5); 6.14 (1H, br. d, J = 13.0 Hz, α-H); 5.84 (1H, d, J = 13.0 Hz, α-H); 4.8-5.0 (1H, two overlapping q, J = 6.8 Hz, $CH_3C\underline{H}$); 1.26 ppm (3H, d, J = 7 Hz, $C\underline{H_3}CH$).

***o*-Iodo-*p'*-methylbenzophenone (XII).** *o*-Iodobenzoic acid chloride (106.6 g, 0.4 mol) was added dropwise with cooling to stirred suspension of anhydrous $AlCl_3$ (88.4 g, 0.66 mol) in dry toluene (220 ml). The reaction mixture was held at room temperature for about 16 h, then for 2 h at 50°C, cooled, and poured onto ice. The obtained product was treated under cooling with conc. HCl (30 ml) and extracted with chloroform. The extract was washed with water, solutions of sodium sulfite and NaOH, and then water, and dried over $CaCl_2$. Evaporation of $CHCl_3$ and toluene and distillation of the residue in vacuo gave ketone XII (57.6 g) as a yellowish oil with bp 185°C/2 mm Hg. On addition of several drops of alcohol and cooling, it crystallized completely; mp 54.5-55°C (alcohol).

***o*-Iodo-*p'*-methyldiphenylmethane (XIII).** Ketone XII (32.2 g, 0.1 mol) According to the method [12] was reducted of using complex of lithium aluminium hydride with aluminium chloride prepared previously from $LiAlH_4$ (6.59 g, 0.17 mol) and $AlCl_3$ (46.73 g, 0.35 mol) in absolute ether. After the usual treatment and distillation in vacuo under argon, the product XIII (22.21 g) was obtained; bp 174-176°C/5 mm Hg, n_D^{20} 1.6288.

3-Methyl-10H-dibenz[b,e]iodinium Tetrafluoroborate (XI). Solution of iodoarene XIII (5.14 g, 16.7 mmol) in Ac_2O (10 ml) was added dropwise under cooling to AcO_2H (27%, 25 ml) and the mixture was held for 12 h at 20°C. Then conc. H_2SO_4 (10 ml) was slowly added dropwise with stirring to the solution of the prepared iodoso derivative XIV at 0°C and the mixture was held for one day at 20°C and then poured onto ice. NH_4BF_4 (17.85 g, 0.17 mol) was added to the obtained solution of 3-methyl-10H-dibenz[b,e]iodinium bisulfate, the reaction mixture stirred, and the product XI extracted from it using $MeNO_2$-$CHCl_3$ (3:1 by volume). The extract was dried, solvents evaporated, and the residue reprecipitated from acetone using ether to give the salt XI (5.48 g). A solution of the latter in CH_2Cl_2 was filtered through thin layer (7-10 mm, d = 15 mm) of alumina and the filtrate evaporated to minimum volume. Addition of ether precipitated the salt XI; mp 163-165°C.

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REFERENCES

1. D. F. Banks, *Chem. Rev.*, **66**, 243 (1966).
2. G. A. Olah, *Halonium Ions*, Wiley Interscience, New York (1975).
3. G. F. Koser, *Chemistry of Functional Groups.* Suppl. D., Wiley Interscience, Chichester (1983), Chapter 25, p. 1265.
4. P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, **96**, 1123 (1996).
5. F. Bickelhaupt, C. Jongsma, P. de Koe, R. Laurens, N. R. Mast, G. L. van Mourik, H. Vermeer, and R. J. M. Weustink, *Tetrahedron*, **32**, 1921 (1976).
6. A. N. Nesmeyanov and T. P. Tolstaya, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, No. 4, 647 (1959).
7. N. W. Alcock and T. C. Weddington. *J. Chem. Soc.*, No. 8, 4103 (1963).
8. J. Collette, D. McGreer, R. Crawford, F. Chubb, and R. B. Sandin, *J. Am. Chem. Soc.*, **78**, 3819 (1956).
9. Z. G. Aliev, L. O. Atovmyan, L. D. Egorova, I. N. Lisichkina, and T. P. Tolstaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 5, 1042 (1985).
10. E. Mohr and Fr. Koehler, *J. Prakt. Chem.*, **80**, 521 (1909).
11. D. Janssen and Ch. Wilson, *p-Iodoveratrole. Synthesis of Organic Substances* [Russian translation], Vol. 8, Inostr. Lit., Moscow (1958), p. 22.
12. J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, No. 3, 1405 (1961).