PREPARATION OF 1-ARYL-2-METHYL-3-CARBETHOXY-4,5-DIOXO-6-BROMOINDOLES*

A. N. Grinev, G. Ya. Uretskaya,
N. V. Arkhangel'skaya, S. Yu. Ryabova,
and T. F. Vlasova

UDC 547.756'728.1

1-Aryl-2-methyl-3-carbethoxy-5-hydroxy-6-bromoindoles are oxidized by nitric acid to 1-aryl-2-methyl-3-carbethoxy-4,5-dioxo-6-bromoindoles, while 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole is converted to the 4,6-dinitro derivative under similar conditions.

Some of the chloro-substituted o-quinones of the indole series that we have previously obtained have anitviral activities [2]. In this connection, we proposed to obtain bromine analogs by the action of nitric acid on 4,6-dihalo-5-hydroxyindoles by following the method for the synthesis of o-quinones of the benzofuran series [3]. However, judging from the analytical data, a mixture of mono- and dibromo-5-hydroxyindoles was obtained in the bromination of 5-hydroxyindole derivatives (for example, I). 1-Methyl(aryl)-2-methyl-3-carbethoxy-5-acetoxy(benzoxy)-6-bromoidoles (V-IX) were obtained in 50-80% yield by bromination of 5-acetoxy- (II,III) and 5-benzoxyindoles (IV) even in the presence of excess bromine. One of these products — indole VII — was previously obtained in [4]. Hydrolysis of acetoxybromides V and VII-IX with an alcohol solution of potassium hydroxide gives 6-bromo-5-hydroxyindoles (X-XIII) in 87-95% yield, from which (R' = Ar) 1-aryl-2-methyl-3-carbethoxy-4,5-dioxo-6-bromoindoles (XIV-XVI) were obtained by nitration in acetic acid. It is interesting that 1,2-dimethyl-3-carbethoxy-5-hydroxy-4,6-dinitroindole (XVII) was formed from 1,2-dimethyl-3-carbethoxy-5-hydroxy-6-bromoindole (X) under the same conditions.

Quinones that do not contain substituents in the 6 position of the indole ring are of definite interest for biological investigations. We therefore subjected 1,2-dimethyl-3-carbethoxy-5-hydroxyindole to diazo coupling with p-nitrobenzenediazonium hydrochloride and obtained 1,2-dimethyl-3-carbethoxy-4-(p-nitrophenylazo)-5-hydroxyindole (XVIII) in high yield. However, we were unable to isolate a 4-amino-5-hydroxyindole derivative by its reduction with sodium hydrosulfite.

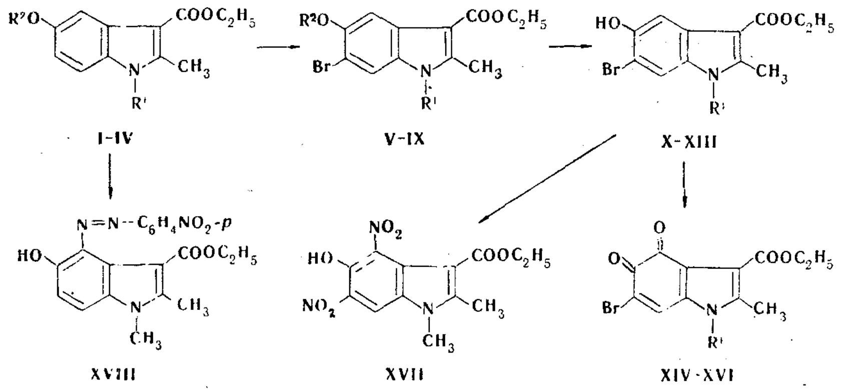
The signals of the protons of the benzene ring in the PMR spectra of V-IX have singlet character, and this provides evidence for bromination in the 6 position. The spectrum 1,2-dimethyl-3-carbethoxy-5-acetoxy-6-bromoindole (V) contains signals at 7.55 and 7.75 ppm that are affiliated with the 4-H and 7-H protons, while the spectrum of 1,2-dimethyl-3-carbethoxy-5-benzoxy-6-bromoindole (VI) contains signals at 7.46 and 7.71 ppm. The spectrum of 1-(p-methoxyphenyl)-2-methyl-3-carbethoxy-5-acetoxy-6-bromoindole (IX) contains a signal at 7.86 ppm that is affiliated with the 7-H proton. The signal of the 4-H proton is overlapped by signals of the phenyl ring protons. Two doublets at 6.54 and 7.28 ppm that are affiliated with the ortho 6-H and

---

*Communication LIV from the series "Research on Quinones." See [1] for Communication LIII.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1379-1381, October, 1974. Original article submitted August 14, 1973.

7-H protons are observed in the spectrum of 1,2-dimethyl-3-carbethoxy-4-(p-nitrophenylazo)-5-hydroxyindole (XVIII) in the region of aromatic protons.



I R^1=CH_3, R^2=H; II, VIII R^1=p-$CH_3C_6H_4$, R^2=CH_3CO; III, IX R^1=p-$CH_3OC_6H_4$, R^2==CH_3CO; IV, VI R^1=CH_3, R^2=$C_6H_5CH_2$; V R^1=CH_3, R^2=CH_3CO; VII R^1=C_6H_5; R^2=CH_3CO; X R^1=CH_3; XI, XIV R^1=C_6H_5; XII, XV R^1=p-$CH_3C_6H_4$; XIII, XVI R^1=p-$CH_3OC_6H_4$

EXPERIMENTAL

The PMR spectra were recorded with JNM-4H-100 and S-60 spectrometers with tetramethylsilane as the internal standard. The solvent for V, VI, and XVIII was deuterochloroform, while deuteroacetone was the solvent for IX. The IR spectra of mineral-oil suspensions of the compounds were recorded with a UR-10 spectrometer.

1-Aryl-2-methyl-3-carbethoxy-5-acetoxyindoles (II,III). A suspension of 15.45 g (0.05 mole) of 1-(p-tolyl)-2-methyl-3-carbethoxy-5-hydroxyindole, 5.1 g (0.05 mole) of acetic anhydride, and 4.8 ml [4.7 g (0.06 mole)] of pyridine was heated at 96-100° for 5 h. The resulting solution was allowed to stand overnight at 18-20°, after which it was poured into water. The resulting precipitate was removed by filtration, washed with 8% hydrochloric acid and water, and dried. The yields and physical constants of the synthesized compounds are presented in Table 1.

1,2-Dimethyl-3-carbethoxy-5-benzoxyindole (IV). A mixture of 14 g (0.06 mole) of hydroxyindole I, 50 g (0.36 mole) of potassium carbonate, and 12.1 g (0.096 mole) of benzyl chloride in 180 ml of acetone was refluxed for 28 h. At the end of the heating period, the acetone was removed by distillation, the residue was refluxed with a mixture of benzene and water, the resulting emulsion was filtered, and the benzene solution was separated, washed with water, and dried with magnesium sulfate. The benzene was removed by distillation, and the residual oily substance was recrystallized from ethyl acetate to give 5.8 g (30%) of a product with mp 103.5-104.5° (from ethyl acetate). Found: C 74.4; H 6.6%. $C_{20}H_{21}NO_3$. Calculated: C 74.3; H 6.6%.

1-Methyl(aryl)-2-methyl-3-carbethoxy-5-acetoxy(benzoxy)-6-bromoindoles (V-IX). A solution of 1 ml [3.12 g (0.02 mole)] of bromine in 25 ml of acetic acid was added dropwise with stirring at 18-20° in the course of 1.5 h to a suspension of 2.75 g (0.01 mole) of 1,2-dimethyl-3-carbethoxy-5-acetoxyindole in 25 ml of acetic acid. During the addition of the bromine solution, the starting material dissolved, and 1,2-dimethyl-3-carbethoxy-5-acetoxy-6-bromoindole began to precipitate. At the end of the addition of the bromine the mixture was stirred for 2.5 h. The precipitate was then removed by filtration, washed with water, and dried (Table 1).

1-Methyl(aryl)-2-methyl-3-carbethoxy-5-hydroxy-6-bromindoles (X-XIII). A suspension of 6.15 g (0.017 mole) of bromoindole V and 32 ml of 10% potassium hydroxide solution in ethanol was refluxed with stirring for 1 h. The mixture was then poured into water, and 15 ml of concentrated HCl was added. The resulting precipitate was removed by filtration, washed with water and dried in a desiccator at 80° (Table 1).

1-Aryl-2-methyl-3-carbethoxy-4,5-dioxo-6-bromoindoles (XIV-XVI). A solution of 0.63 ml [0.85 g (0.007 mole)] of nitric acid (sp. gr. 1.35) in 7.5 ml of acetic acid

TABLE 1. Physical Constants and Yields of the Compounds Obtained

Compound	mp, °C	Empirical Formula	Found, %			Calc., %			Yield %
			C	H	Br	C	H	Br	
II	146—147[b]	$C_{21}H_{21}NO_4$	71,5	6,0	—	71,8	6,0	—	100
III	122—123,5[a]	$C_{21}H_{21}NO_5$	68,5	5,8	—	68,6	5,8	—	97
V	174—175[a]	$C_{15}H_{16}BrNO_4$	50,7	4,5	23,0	50,9	4,5	22,6	86
VI	116,5—118[a]	$C_{20}H_{20}BrNO_3$	59,5	5,0	19,7	59,7	5,0	19,9	50
VIII	129,5—130,5[a]	$C_{21}H_{20}BrNO_4$	58,9	4,9	18,4	58,6	4,7	18,6	81
IX	161—162[c]	$C_{21}H_{20}BrNO_5$	56,4	4,6	17,9	56,5	4,5	17,9	60
X	219,5—220[d]	$C_{13}H_{14}BrNO_3$	50,0	4,4	25,3	50,0	4,5	25,6	95
XI	185—186,5[a]	$C_{18}H_{16}BrNO_3$	57,6	4,5	21,4	57,8	4,3	21,4	92
XII	217,5—218 (dec.)[a]	$C_{19}H_{18}BrNO_3$	58,8	4,8	20,6	58,8	4,7	20,6	87
XIII	215—217[a]	$C_{19}H_{18}BrNO_4$	56,6	4,5	19,5	56,5	4,5	19,8	92
XIV	176—178[e]	$C_{18}H_{14}BrNO_4$	55,9	3,5	20,4	55,7	3,6	20,6	96
XV	196,5—198,5[e]	$C_{19}H_{16}BrNO_4$	56,7	3,9	20,0	56,7	4,0	19,9	65
XVI	201—202[e]	$C_{19}H_{16}BrNO_5$	54,6	3,8	19,0	54,6	3,9	19,1	84

---

*a) From alcohol. b) From methanol. c) From cyclohexane—CCl_4. d) From dichloroethane. e) From ethyl acetate.

was added dropwise at 16-18° in the course of 25 min to a suspension of 1.85 g (0.005 mole) of bromoindole XI in 30 ml of acetic acid, during which the white precipitate gradually dissolved and a brown precipitate formed. At the end of the addition of nitric acid, the mixture was stirred for 2.5 h. The precipitate was then removed by filtration, washed with water, and dried. The IR spectra did not contain an absorption band at 3200-3400 cm^{-1} (OH), but there were three absorption bands at 1670-1720 cm^{-1} (CO) (Table 1).

1,2-Dimethyl-3-carbethoxy-5-hydroxy-4,6-dinitroindole (XVII). A solution of 0.9 ml [1.2 g (0.01 mole)] of nitric acid (sp. gr. 1.35) in 7.5 ml of acetic acid was added dropwise at 17-19° with stirring in the course of 30 min to a suspension of 1.6 g (0.005 mole) of bromoindole X in 33 ml of acetic acid, during which the white solid dissolved and a brown precipitate formed. At the end of the addition of the nitric acid, the mixture was stirred for another 2 h, and the precipitate was removed by filtration and washed with water. The filtrate was washed with water, and the resulting precipitate was removed by filtration, washed with water, and added to the precipitate obtained from the reaction mixture. The product was air dried to give 0.95 g (57.5%) of a material with mp 228-228.5° (from dioxane—alcohol). Found: C 48.2; H 3.9; N 12.8%. $C_{13}H_{13}N_3O_7$. Calculated: C 48.3; H 4.0; N 13.0%.

1,2-Dimethyl-3-carbethoxy-4-(p-nitrophenylazo)-5-hydroxyindole (XVIII). A solution of p-nitrobenzediazonium chloride prepared from 3.6 g (0.026 mole) p-nitroaniline, 6 ml of concentrated HCl, 38 ml of water, and a saturated aqueous solution of 2 g (0.029 mole) of sodium nitrite, was added dropwise with stirring at 0° to a solution of 4.6 g (0.02 mole) of hydroxyindole I in 30 ml of dioxane and 40 ml of 5% sodium hydroxide solution. The mixture was stirred at 0-5° for 3 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 7.4 g (97%) of a product with mp 200-202° (decomp., from benzene.). Found: C 60.3; H 4.7; N 14.4%. $C_{19}H_{18}N_4O_5$. Calculated: C 59.7; H 4.7; N 14.6%.

LITERATURE CITED

1. A. N. Griner, N. V. Arkhangel'skaya, and G. Ya. Uretskaya, Khim. Farmats. Zh., No. 5, 3 (1972).
2. A. N. Grinev, G. Ya. Uretskaya, and S. F. Liberman, Khim. Geterotsikl. Soedin., 335 (1971).
3. A. N. Grinev, N. V. Arkhangel'skaya, and G. Ya. Uretskaya, USSR Author's certificate No. 361173; Byul. Izobret., No. 1, 57 (1973).
4. A. N. Kost, L. G. Yudin, and E. Ya. Zinchenko, Khim. Geterotsikl. Soedin., 333 (1973).