INDOLE CHEMISTRY

XXVI.* MERCURATION OF 1-METHYLINDOLES

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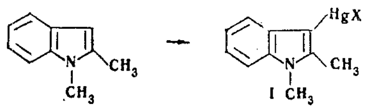
1-Methylindoles are smoothly mercurated with substitution of the hydrogen atoms in the 3 position of the pyrrole ring. If, however, the latter is occupied, they are substituted in the 2 position. The resulting 2- or 3-chloromercuriindoles are readily converted to symmetrical diindolylmercury compounds, and the chloromercuri group is replaced by iodine and acyl groups; in the presence of palladium salts, they react with acrylic acid esters to form indolylacrylic acid esters.

Of the electrophilic substitution reactions in the indole series, mercuration has received very little study. This is apparently explained by the unsuccessful attempts of a number of investigators, who obtained infusible and insoluble polymercuration products by the action of mercury salts on indole [2-4]. However, 1-methyl-3-iodo-2-chloromercuriindole, synthesized by an indirect route – decarboxylation of the mercury salt of 1-methyl-3-iodoindole-2-carboxylic acid – has a sharp melting point and properties that are typical for arylmercury chlorides [5].

It is known that mercuration of the benzene ring proceeds with relative difficulty, often under pressure, while pyrrole, furan, and thiophene readily undergo mercuration at room temperature [6]. It was therefore difficult to assume that the products of the polymercuration of indole are formed through substitution of the hydrogen atoms of the benzene ring. In fact, it has been reported [7] that the mercuration of indole by mercury acetate in alcohol gives a dimercury compound in which both acetoxymercuri groups are situated in the heterocyclic portion of the molecule; the structure of the compound was not more accurately established, however.

We have performed a number of experiments on the mercuration of indole and its homologs and have found that indoles with a free NH group actually form hard-to-purify products of di- and polymercuration, the IR spectra of which do not contain the absorption band characteristic for the NH group. (We did not investigate them in greater detail.)

If, however, 1-methylindoles are introduced into the reaction, the pyrrole portion of the indole ring is mercurated to give easily identifiable compounds. Thus the action of mercury acetate in methanol or of mercuric chloride in the presence of sodium acetate on 1,2-dimethylindole gives a quantiative yield of 1,2-dimethyl-3-mercuriindole (I).



X = OCOCH$_3$, Cl

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* See [1] for communication XXV.

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TABLE 1. Mercurated Compounds of the Indole Series

Compound	mp, °C (solvent)	R_f	Empirical formula	Found, %		Calc., %		Yield, %
				C	H	C	H	
1,2-Dimethyl-3-chloromercuriindole	194—196 (ethyl acetate)	0,31*	$C_{10}H_{10}ClHgN$	31,6 31,6	3,0 2,9	31,6	2,6	98
1,3-Dimethyl-2-chloromercuriindole	248—250 (toluene)	0,75†	$C_{10}H_{10}ClHgN$	31,3 31,4	2,9 2,8	31,6	2,6	83
1-Methyl-3-chloromercuriindole	170—173 (benzene)	0,32†	C_9H_8ClHgN	29,8 29,7	2,3 2,3	29,5	2,2	80
1-Acetyl-3-chloromercuriindole	236—238 (alcohol)	0,37†	$C_{10}H_8ClHgNO$	30,9 30,7	2,1 2,1	30,5	2,0	87
1-Methyl-2-acetyl-3-chloromercuriindole	196—199 (toluene)	0,52†	$C_{11}H_{10}ClHgNO$	32,5 32,6	2,7 2,9	32,4	2,5	90
1-Methyl-3-acetyl-2-chloromercuriindole	293—296 (toluene)	0,21†	$C_{11}H_{10}ClHgNO$	32,7 32,5	2,6 2,5	32,4	2,5	20
1,2-Dimethyl-5-nitro-3-chloromercuriindole	290—293 (ethyl acetate)	0,57*	$C_{10}H_9ClHgN_2O_2$	28,4 28,2	2,3 2,0	28,2	2,1	92
1-Methyl-2,3-di-(chloromercuri)indole	300 (dec.,acetone)	—	$C_9H_7Cl_2Hg_2$	17,5 17,7	1,3 1,2	18,0	1,2	12

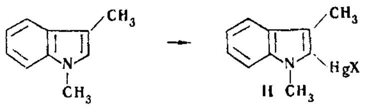
*Benzene—ethyl acetate (2 : 1).

†Benzene—ethyl acetate (6 : 1).

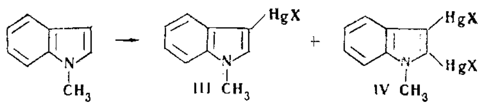
TABLE 2. Diindolylmercury Derivatives

Compound	mp, °C (solvent)	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
Bis(1,2-dimethyl-3-indolyl)-mercury	208—209 (ethyl acetate)	$C_{20}H_{20}HgN_2$	49,0 49,2	4,5 4,4	48,9	4,5	95
Bis(1,3-dimethyl-2-indolyl)-mercury	257 (toluene)	$C_{20}H_{20}HgN_2$	49,0 48,7	4,3 4,3	48,9	4,5	98
Bis(1-methyl-3-indolyl)-mercury	123—124 (toluene)	$C_{18}H_{16}HgN_2$	46,7 46,9	3,8 3,6	46,9	3,5	90
Bis(1-acetyl-3-indolyl)-mercury	246—247 (ethyl acetate)	$C_{20}H_{16}HgN_2O_2$	46,7 46,9	3,5 3,5	46,5	3,1	99
Bis(1-methyl-2-acetyl-3-indolyl)mercury	250 (toluene)	$C_{22}H_{20}HgN_2O_2$	48,7 48,9	3,7 3,5	48,5	3,7	92
Bis(1-methyl-3-acetyl-2-indolyl)mercury	279—281	$C_{22}H_{20}HgN_2O_2$	48,3 48,7	3,8 3,6	48,5	3,7	90

Similarly, 1,3-dimethylindole is readily mercurated in the α position to form II:

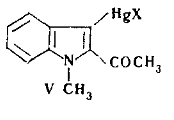


The reaction proceeds in a somewhat more complex fashion for 1-methylindole, in which 1-methyl-2,3-diacetoxymercuriindole (IV) is formed along with the corresponding 1-methyl-3-acetoxymercuriindole (III):

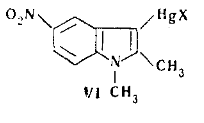


The PMR spectrum of III does not contain a signal for the β proton of the indole ring at 6.5 ppm, and this confirms its structure.

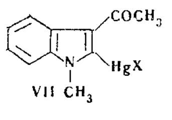
The introduction of electron-acceptor groups into the pyrrole or benzene rings does not substantially restrict the mercuration. Thus 1-methyl-2-acetylindole and 1,2-dimethyl-5-nitroindole are mercurated without complications in the 3 position to form V and VI, while 1-methyl-3-acetylindole is mercurated in the 2 position to give VII. However, the latter reaction proceeds under more severe conditions (refluxing for 24 h in alcohol) and gives lower yields (20%), which is probably associated not only with the reduced electron density in the 2 position but also with steric hindrance.



V



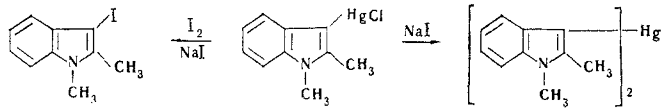
VI



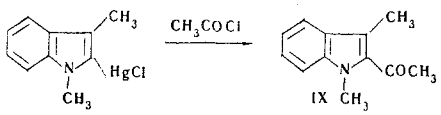
VII

The mercuration of 1-acetylindole yielded 1-acetyl-3-chloromercuriindole (VIII), the PMR spectrum of which does not contain a signal for the β proton at 6.5 ppm. A more accurate assignment of the mercury compounds to the α or β series was also made on the basis of a comparative study of their ability to undergo electrochemical reduction, which has already been reported [8].

All of the compounds that we obtained (Table 1) are readily converted to symmetrical diindolylmercury derivatives (Table 2) by the action of sodium iodide in acetone. Chloromercuriindoles I-III, V, and VIII are converted in good yields to the corresponding iodoindoles by the action of an aqueous solution of iodine and sodium iodide.

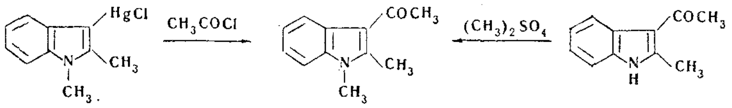


The chloro or acetoxymercury group is replaced by an acyl group by the reaction of I and II with acetyl chloride or benzoyl chloride in absolute benzene. However, the yields of 1,2-dimethyl-3-acetyl-(X) and 1,3-dimethyl-2-acetylindole (IX) [9] were insignificant at both room temperature and on refluxing. 1,2-Dimethyl- and 1,3-dimethylindoles were detected in the reaction mass by chromatography. After several hours at room temperature without a solvent, both acetyl chloride and benzoyl chloride give 70-90% yields of α-acylation products with 1,3-dimethyl-2-chloromercuriindole:



IX

The yields of acylation products are low (10-15%) for 1,2-dimethyl-3-chloromercuriindole ever under these conditions:



In a study of the kinetics of the protodemercuration of I, II, V, and VII in alcohol and aqueous dioxane solutions of hydrogen chloride and perchloric acid, it was found that a C–Hg bond in the β position of the indole ring (regardless of the substituent) is more reactive than in the α position [10]. A detailed study of the kinetics of the protolysis of mercurated indoles will be the subject of a separate study.

Compounds I and II react with methyl acrylate in the presence of palladium salts (just as described for a number of other arylmercury chlorides [11]). Methyl indolylacrylate (XI) was obtained from 1,3-dimethyl-2-chloromercuriindole. Methyl β-(1,2-dimethyl-3-indolyl)acrylate was obtained in 10-15% yield from the β isomer.

A preliminary communication regarding the mercuration of indole was published in [12].

EXPERIMENTAL

The purity of the indoles was monitored by chromatography in a loose, thin layer of activity II aluminum oxide with benzene as the solvent. The purity of the chloromercuriindoles was monitored by chromatography on Silufol (UV-254). The PMR spectra of dimethyl sulfoxide solutions were recorded with an RS-60 spectrometer.

1,3-Dimethyl-2-chloromercuriindole (II). A solution of 2.72 g (0.01 mole) of mercuric chloride and 4.48 g (0.04 mole) of sodium acetate in 100 ml of aqueous methanol was added to a solution of 1.45 g (0.01 mole) of 1,3-dimethylindole in 20 ml of methanol, and the mixture was stirred for several hours at room temperature. The precipitate was removed by filtration, and the filtrate was poured into water. The resulting precipitate was combined with the first precipitate and washed with water, air-dried, and washed with ether to give 3.3 g (83%) of II with mp 248-250° (from alcohol). Found: C 31.3; 31.4; H 2.9; 2.8%. $C_{10}H_{10}ClHgN$. Calculated: C 31.6; H 2.6%.

The compounds listed in Table 1 were similarly obtained.

Bis(1,2-dimethyl-3-indolyl)mercury (XIII). A tenfold excess of sodium iodide was added to a solution of 1.6 g (0.005 mole) of 1,2-dimethyl-3-chloromercuriindole (I) in 20 ml of acetone. After several minutes, the reaction mixture was treated with water, and the precipitate was removed by filtration, washed with water, dried, and washed with ether to give 0.9 g (88%) of XIII with mp 208-209° (from benzene). Found: C 49.0; 49.2; H 4.4; 4.5%. $C_{20}H_{20}HgN_2$. Calculated: C 48.9; H 4.5%.

The compounds listed in Table 2 were similarly obtained.

1,2-Dimethyl-3-iodoindole (XIV). A 3.8-g (0.01 mole) sample of chloromercuriindole I was added to a solution of 2.45 g (0.01 mole) of iodine in an aqueous solution of sodium iodide, and the mixture was stirred at room temperature for 2 h and filtered. The precipitate was washed with aqueous sodium iodide and water, dried, and dissolved in ether. The ether solution was passed through aluminum oxide with elution by benzene. The solvent was removed by distillation in vacuo, and the residue was recrystallized from light petroleum ether to give 1.5 g (56%) of XIV with mp 80-83° (dec.) and R_f 0.87. Found: C 44.0; 44.0; H 3.7; 3.8%. $C_{10}H_{10}IN$. Calculated: C 44.3; H 3.7%.

1,3-Dimethyl-2-iodoindole. This compound (42%) was similarly obtained and had mp 64-66° and R_f 0.87. Found: C 43.8; 44.0; H 3.7; 3.8%. $C_{10}H_{10}IN$. Calculated: C 44.3; H 3.7%.

1-Methyl-2-acetyl-3-iodoindole. This compound (98%) was similarly obtained and had mp 113° and R_f 0.80. Found: C 44.1; 44.1; H 3.4; 3.3%. $C_{11}H_{10}INO$. Calculated: C 44.1; H 3.3%.

1-Acetyl-3-iodoindole. This compound (78%) was similarly obtained and had mp 104° and R_f 0.78. Found: C 41.9; 42.0; H 2.8; 2.9%. $C_{10}H_8INO$. Calculated: C 42.1; H 2.8%.

1,3-Dimethyl-2-acetylindole (IX). A total of 30 ml of freshly distilled (over dimethylaniline in a stream of nitrogen) acetyl chloride was added to 3.8 g (0.01 mole) of 1,3-dimethyl-2-chloromercuriindole (II). After several minutes, the solid began to dissolve with heat evolution. When the solid had dissolved completely, the acetyl chloride was removed by vacuum distillation. The residue was washed with aqueous sodium bicarbonate, filtered, washed with water, and recrystallized from petroleum ether to give 1.3 g (72%) of IX with mp 78-79° (from petroleum ether) and R_f 0.63. Found: C 77.0; 77.2; H 7.0; 7.2%. $C_{12}H_{13}NO$. Calculated: C 77.0; H 7.0%.

1,3-Dimethyl-2-benzoylindole (XV). A total of 30 ml of freshly distilled (over chalk) benzoyl chloride was added to 6 g (0.015 mole) of 1,3-dimethyl-2-acetoxymercuriindole, and the mixture was heated at 40° for several minutes, during which the solid dissolved rapidly. The reaction mixture was allowed to stand at room temperature for several hours. It was then poured into water and treated with ammonium hydroxide. The precipitate was washed with hot water and crystallized from petroleum ether to give a product with mp 68-69° and R_f 0.76. Found: C 82.4; 82.3; H 6.2; 6.2%. $C_{17}H_{15}NO$. Calculated: C 82.0; H 6.0%.

Methyl β-(1,3-Dimethyl-2-indolyl)acrylate (XI). Lithium chloride [0.58 g (0.014 mole)] and 1.21 g (0.007 mole) of palladium chloride were added to 50 ml of absolute methanol, and the mixture was stirred for 24 h at room temperature. 1,3-Dimethyl-2-chloromercuriindole [2 g (0.005 mole)] was added, and 8 g (0.093 mole) of methyl acrylate was added dropwise with stirring to the mixture. The mixture was then stirred for 48 h at room temperature, and the precipitate was removed by filtration. The methanol was removed by vacuum distillation, and the residue was recrystallized from petroleum ether to give 0.52 g (43%) of XI with mp 105-106° and R_f 0.76. Found: C 73.6; 73.4; H 6.7; 6.7%. $C_{14}H_{15}NO_2$. Calculated: C 73.4; H 6.6%.

Methyl β-(1,2-dimethyl-3-indolyl)acrylate with mp 162° and R_f 0.17 was similarly obtained. Found: C 73.7; 73.5; H 6.7; 6.5%. $C_{14}H_{15}NO_2$. Calculated: C 73.4; H 6.6%.

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