EXPERIMENTAL[3]

2-Trifluoromethyl-5-nitrofuran. 5-Nitro-2-furoic acid (15.7 g., 0.1 mole) was placed in a 183 ml. stainless steel bomb, which was sealed and cooled in an acetone–Dry Ice bath. After evacuation to about 0.3 mm. pressure, the vessel was charged with sulfur tetrafluoride[4] (43 g., 0.4 mole). After allowing the mixture to warm to room temperature, the reactor was heated to 120° for 7 hr. under autogenous pressure. Following the reaction the cooled bomb was vented and the oily residue taken up in chloroform. The chloroform extract was washed with sodium carbonate solution followed by water, then dried and the solvent removed. The residual oil was fractionally distilled to give 5.47 g. of a light yellow liquid with a camphor-like odor, b.p. 108° (102 mm), n_D^{25} 1.4368. When the sodium carbonate extract was neutralized with acetic acid and cooled, 3.5 g. of the sodium salt of 5-nitro-2-furoic acid (explodes at 247°) was obtained. Based on recovered starting material the yield of pure trifluoromethyl compound was 37%.

Anal. Calcd. for $C_5H_2F_3NO_3$: C, 33.16; H, 1.11; N, 7.74. Found: C, 33.39; H, 1.39; N, 7.60.

2-Difluoromethyl-5-nitrofuran. Sulfur tetrafluoride (42 g., 0.39 mole) was added to 5-nitro-2-furaldehyde (26.4 g., 0.187 mole) in the manner described above. After heating for 8 hr. at 65°, the bomb was cooled and vented. The residue was worked up as before and distilled to provide 6.7 g. of the difluoromethyl compound, b.p. 96–98° (13 mm), $n_D^{21.3}$ 1.4910–1.4922 and 6.2 g. of starting nitrofuraldehyde. Based on recovered starting material the yield was 28%.

Anal. Calcd. for $C_5H_3F_2NO_3$: C, 36.82; H, 1.85; N, 8.59. Found: C, 36.88; H, 1.99; N, 8.56.

2-(α,α-Difluoroethyl)-5-nitrofuran. A mixture of 2-acetyl-5-nitrofuran (31 g., 0.2 mole) and water (1 ml.) was charged with sulfur tetrafluoride (63.0 g., 0.575 mole) as described above. The addition of water was necessary in order to generate hydrofluoric acid to catalyze the reaction. After heating at 75° for 10 hr., the reaction was worked up in the usual way to give 8.9 g. (25%) of the difluoroethyl derivative b.p. 58–60° (0.5 mm.), n_D^{25} 1.4717. When the reaction was carried out at 55–60° for 10 hr., the yield was increased to 34%.

Anal. Calcd. for $C_6H_5F_2NO_3$: C, 40.68; H, 2.84; N, 7.91. Found: C, 40.81; H, 3.09; N, 7.98.

In an attempt to prepare the difluoroethyl compound by carrying out the reaction with catalyst at 40° for 10 hr. only starting ketone was recovered, in 70% yield. When the reaction was run at 75° for 10 hr. in the absence of catalyst, starting material was again recovered, this time in 50% yield. At 110° only tars were formed.

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(3) Boiling and melting points are uncorrected. Analyses were carried out by E. F. Shelberg and staff of Abbott Laboratories.

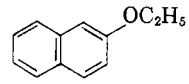
(4) Purchased from E. I. du Pont de Nemours and Company.

Novel Synthesis of Heterocyclic Ketones

WILLIAM C. ANTHONY

Received March 3, 1960

The introduction of an aldehyde function into aromatic (I)[1] and heterocyclic (II)[2] compounds

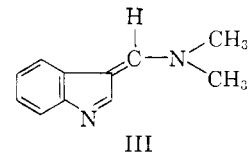


I

II

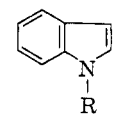
by use of phosphorus oxychloride and methyl formanilide or dimethylformamide has been described in the literature. In this paper we report the introduction of a ketone function into certain indoles and pyrroles by means of phosphorus oxychloride and the appropriate amide. The compounds which were prepared by this method are listed in Table I. All attempts to acylate β-ethoxynaphthalene, thiophene, dimethylaniline, and fluorene by this method failed.

It has been stated[1] that only *one* replaceable hydrogen on the aromatic system is necessary for the reaction with formamides to proceed. Smith[3] has applied this procedure to the preparation of indole-3-carboxaldehyde. He isolated and characterized the intermediate III and proposed a reaction mechanism which would require two replaceable hydrogens on the nucleophile.



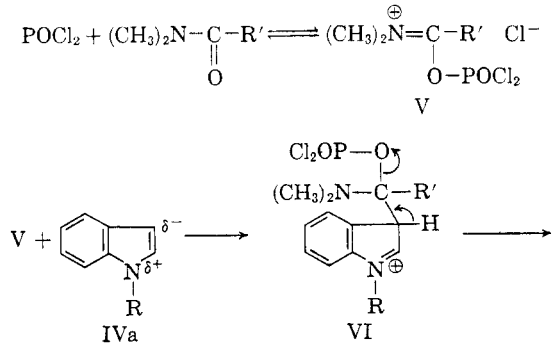
III

In the course of our investigation of indole and pyrrole ketone formations, we have found that an indole compound (IV) with only one replaceable hydrogen, is also convertible into a ketone. With such a starting material, an intermediate similar to III is not possible.



IV R = ethyl

The following reaction scheme may apply to acylations of indoles and pyrroles which contain either one or two replaceable hydrogens:



V

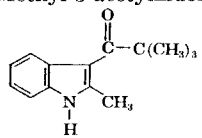
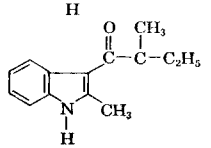
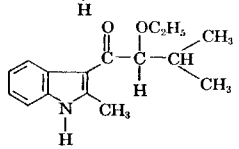
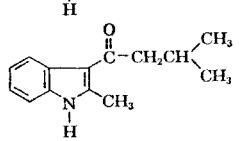
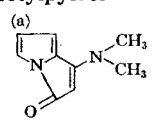
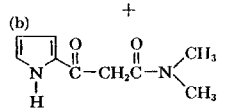
IVa VI

(1) *Org. Syntheses*, Coll. Vol. III, 98 (1955).

(2) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, **75**, 989 (1953).

(3) G. F. Smith, *J. Chem. Soc.*, 3842 (1954).

TABLE I

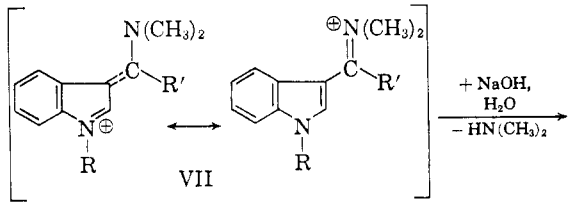
	Nucleophile	Electrophile	Product	M.P.	Yield, %	C,% Calcd.	C,% Found	H,% Calcd.	H,% Found	Z,% Calcd.	Z,% Found	Recrystallization Solvent
1.	5-Benzyl oxy-indole	*N,N*-Dimethylacetamide	5-Benzyloxy-3-acetylindole	189–190[a]	71							95% Ethanol
2.	Indole	*N,N*-Dimethylpropionamide	3-Propionylindole	171–173[a]	85.5							Benzene-petroleum ether, b.p. 60–71°
3.	Indole	*N,N*-Dimethylchloracetamide	3-Chloroacetylindole	233–234[b]	36.6							95% Ethanol
4.	Indole	*N,N*-Dimethylbenzamide	3-Benzoylindole	241–243.5[c]	51	81.42	81.35	5.01	5.03	6.33	6.39	95% Ethanol
5.	Indole	*N*-Methylacetamide	3-Acetylindole	191–193[d]	22.4							95% Ethanol
6.	2-Methylindole	*N,N*-Dimethylacetamide	2-Methyl-3-acetylindole	195–196[e]	98.0							95% Ethanol
7.	2-Methylindole	*N,N,α,α,α*-Pentamethylacetamide		134–135	49.0	78.11	78.20	7.94	8.53	6.50	6.32	Benzene-petroleum ether, b.p. 60–71°
8.	2-Methylindole	*N,N,α*-Trimethylbutyramide		101–103	18.0	78.11	78.01	7.94	8.28	6.50	6.28	Petroleum ether, b.p. 60–71°, 95% ethanol
9.	2-Methylindole	*α*-Ethyl-*N,N,β*-trimethylbutyramide		106–109	24.0	78.92	78.97	8.65	9.11	5.75	5.74	95% Ethanol
10.	2-Methylindole	*N,N*-Dimethylisovaleramide		139–141	62	78.09	78.21	7.56	7.85	6.50	6.35	95% Ethanol
11.	1-Ethylindole	*N,N*-Dimethylacetamide	1-Ethyl-3-acetylindole	87–89[f]	76							95% Ethanol
12.	Pyrrole	*N,N*-Dimethylacetamide	2-Acetylpyrrol	91–92[g]	49							Pet.ether, b.p. 60–71°
13.	Pyrrole	*N,N,N',N'*-Tetramethylmalonamide	(a)  + (b) 	143–144 B.p. 154°/ 1 mm.	6 Undetermined	66.58 59.42	66.99 60.28	6.21 6.71	6.03 6.24	17.27 15.54	17.20 15.73	Benzene

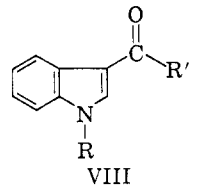
[a] Identical with a sample prepared according to the method described by J. Szmuszkovicz in *J. Am. Chem. Soc.*, 82, 1180 (1960). [b] D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.* (1956) 1958. [c] Bernardo Oddo and Fuigi Sessa, *Gazz. Chim. Italia*, 41, I, 243 (1911). [d] Carlo Zatti, *Ber.*, 22, 662 (1889). [e] O. R. Jackson, *Ber*, 14, 880 (1881). [f] Yu A. Baskakov and N. N. Meljnikov Solbrnik, *Sbornik Statei Obshchei Khim., Akad. Nauk, U.S.S.R.*, 1, 712–713 (1953). [g] Robert Schiff, *Ber.*, 10, 1501 (1877).

TABLE II

ABSORPTION SPECTRA OF NEW COMPOUNDS PREPARED

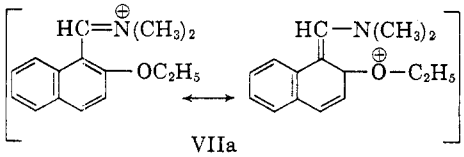
Compd. No.	Infrared, cm.$^{-1}$	Ultraviolet, mμ (ϵ) 95% ethanol
4	NH (3085); C=O (1595); amide vinylog (1565); C=C (1515, 1490); aromatic (747, 713, 697)	313 (12,000); 266 (10,550); 247 (15,075); 303 (14,325); 260 (10,975); 243 (15,400); 206 (47,935)
7	NH (3140); C=O (1592); C=C (1574, 1560, 1527, 1483); C—N (1270, 1205, 1128, 1058, 990); aromatic (795, 752, 740, 720)	302 (10,300); 270 (9,525); 244 (10,675); 216 (29,300)
8	NH (3150, 3080sh); C=O (1592); C=C (1573, 1523, 1485); C—N (1173, 1147, 973); aromatic (785, 751, 747, 735)	301 (10,725); 269 (9,900); 244 (11,675); 216 (29,600)
9	NH (3280); C=O [(plus C=C) 1613]; C=C (1585, 1573, 1485); vinylog (1520); C—N (1267, 1172, 1110); aromatic (757, 738, 728, 700)	303 (11,800); 269.5 (10,375); 245 (11,975); 216 (31,000)
10	NH (3230); C=O (1625, 1610); C=C (1580 sh., 1532, 1492); C—N (1260, 1178, 1052); aromatic (757, 743, 728)	301 (11,450); 268 (10,600); 243 (12,850); 215 (29,400)
13	(a) NH/OH (absent); C=O (1687); C=C (1615, 1357); aromatic (13070); (748, 740sh, 713, 677); other bonds (1430, 1408, 1310, 1250, 1240, 1160, 1073)	431 (2,113); 308 (12,650); (16,375); 274 (15,010); 212 (13,547)
	(b) NH/OH (3200); 6μ region (1680sh, 1655sh, 1625, 1610sh, 1545sh); other bonds (1131, 1107, 1050, 920, 750)	433 (357); 292 (16,269)





R = H or alkyl
R' = alkyl or aryl

A comparison between the behavior of pyrrole and other systems such as β-ethoxynaphthalene in this type of acylation reaction is informative. Although the latter form only aldehydes, the former give both aldehydes and ketones. Furthermore, intermediates such as III have been isolated in the synthesis of compounds containing a pyrrole nucleus but not with other systems. Even in the acetylation of indoles and pyrroles with *N,N*-dimethylcarboxamides, a water soluble compound is formed when water is added to the reaction mixture. This fact lends support to the intervention of intermediates such as VII in the reaction sequence. The counterpart of this intermediate in reactions such as the formylation of β-ethoxynaphthalene would be VIIa. Unlike VII, which probably is sufficiently stabilized by resonance to permit its detection, VIIa may be expected to hydrolyze much more rapidly. The failure of β-ethoxynaphthalene to acetylate with *N,N*-dimethylacetamide is attributable to the relatively low nucleophilicity and higher steric requirements in the former compound.



When this work was essentially complete the existence of German Patent **614,326** was brought to our attention. This patent claims the preparation of 1-methyl-3-*p*-chlorobenzoylindole using *p*-chlorobenzanilide and 1-methylindole. We applied the German procedure to the preparation of 3-acetylindole and found that the procedure reported in this paper is superior to the patented method as the yields were much better and the isolation and purification of the product was simpler. In addition, considerably less time is required to obtain the product.

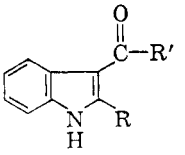
In the course of these experiments some interesting chemical and physical properties of the indolic ketones were observed. It was found that when a carbonyl group is attached to the indole nucleus in the 3-position, the 1-position can be readily alkylated with an alkyl halide and potassium carbonate.[4] When the side chain of the indole ketone was branched, *N*-alkylation could not be achieved under these mild conditions, but could be achieved using much stronger basic conditions.[5]

In the ultraviolet region an alcoholic solution of a 1-unsubstituted 3-acyl indole exhibits a new maximum at 332 mμ in the presence of alkali which is an indication of the degree of enolization. When the 2-position is substituted, branching in the side chain lowers the intensity at this wave length until

(4) W. B. Whalley, *J. Chem. Soc.*, 1651 (1954).
(5) Hans Plieninger, *Ber.*, **87**, 127 (1954).

TABLE III

ULTRAVIOLET ABSORPTIVITY OF[a]

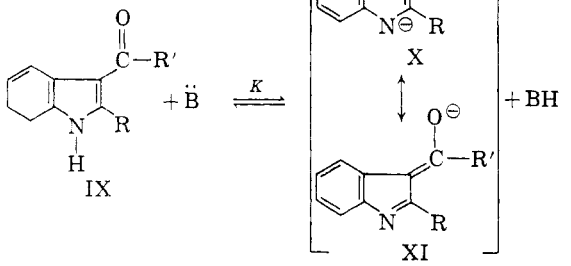


Compd. No.	R	R′	a_M Neutral	a_M KOH	a_M KOH/a_M neutral
5	H	$-CH_3$	483	4750	13.95
2	H	$-CH_2CH_3$	216	2435	11.25
6	$-CH_3$	$-CH_3$	515	1275	2.48
10	$-CH_3$	$-CH_2CH(CH_3)_2$	781	1334	1.71
7	$-CH_3$	$-C(CH_3)_3$	1225	1700	1.38
11[b]	H	$-CH_3$	1071	1047	0.98

[a] (Table I) at 332 mμ (ε) in 95% ethanol and in 0.01*N* 95% ethanolic potassium hydroxide. [b] The compound has a 1-ethyl substituent.

it approaches the value observed in neutral solution as shown in Table III.

The difference in ease of alkylation of the ketones in Table III can be explained on the basis of differences in the degree of steric inhibition of resonance for the various compounds and their respective anions.



The value of K depends on the size of R and R′. If R and R′ are large, then XI is destabilized relative to IX since all the groups cannot become coplanar. Thus the acyl indole becomes a weaker acid, and the value of K is diminished. As a result, a stronger base is needed to effect alkylation. The ultraviolet absorption data of Table III supports this contention.

EXPERIMENTAL[6,7]

The necessary amides which were utilized in this investigation were obtained commercially or were prepared according to literature procedures and used in their crude state. The ketones were prepared essentially as described in the following examples.

5-Benzyloxy-3-acetylindole (I). An 18-ml. sample of *N,N*-dimethylacetamide was cooled to 5° and 7.0 ml. (0.072 mole) of phosphorus oxychloride was slowly added keeping the temperature below 20°. After the addition was complete, a solution of 12.5 g. (0.056 mole) of 5-benzyloxyindole and 9 ml. of *N,N*-dimethylacetamide was slowly added keeping the temperature below 40°. The mixture was heated to 87° for 2 hr. and allowed to cool. The red mass was dissolved in water and extracted with ether. The water solution was made basic with sodium hydroxide and filtered. The solid was washed well with water, refluxed in alcohol containing Darco "60" and filtered. Upon cooling the solution deposited 10.5 g. (71%) of product, m.p. 189–190°. This solid caused no depression in melting point when mixed with an authentic sample (see Table I, footnote *a*).

3-Benzoylindole (4). A mixture of 14 ml. (0.15 mole) of phosphorus oxychloride, 36 g. (0.24 mole) of *N,N*-dimethylbenzamide and 13.0 g. (0.122 mole) of indole was heated to 84° for 2 hr., cooled, and dilute sodium hydroxide was added. The mixture was stirred until a fine suspension was obtained and then filtered. The solid was thoroughly extracted with alcohol to yield 13.5 g. (51%) of product, m.p. 241–243.5°.

Reaction of pyrrole and N,N,N′,N′-tetramethylmalonamide (13). A 93-g. (0.57 mole) sample of phosphorus oxychloride was slowly added to 47.4 g. (0.3 mole) of *N,N,N′,N′*-tetramethylmalonamide at 10–20°. The mixture was cooled to 10° and 20.1 g. (0.3 mole) of pyrrole was slowly added keeping the temperature below 45°. After the addition was complete the mixture was heated over 45 min. to 55–60°. The mixture was maintained at this temperature for 30 min., then cooled and poured into ice water. The solution was made basic with sodium hydroxide and filtered. The solid (7.9 g.) was washed well with water and dried. The solid was shaken twice with 300 ml. of ether and filtered. The ether solution was concentrated yielding 3.5 g. of residue. After three recrystallizations from benzene compound no. 13a was obtained, m.p. 143–144°.

The original basic solution was extracted with ether for 24 hr. and concentrated yielding 16.2 g. of an oil. The oil was dissolved in ether, with a trace of ethyl acetate, and treated with anhydrous hydrogen chloride. The precipitate was washed with ether until free of acid and then treated with potassium hydroxide solution. The mixture was extracted with ethyl acetate. Concentration of the organic layer

(6) All melting points were taken by capillary and are uncorrected.

(7) The author wishes to express his appreciation to Drs. Jacob Szmuszkovicz and R. V. Heinzelman of our Department of Chemistry for their helpful discussions and advice in this work and to Professor D. J. Cram of the University of California, Los Angeles, for his criticisms of and assistance in preparing this paper. The author is also indebted to Dr. J. L. Johnson and associates for spectral data and Mr. W. A. Struck and staff for analytical determinations.

yielded an orange colored oil. A sample of the oil was distilled at 154°/1 mm. to yield compound no. 13b.

Supporting evidence for structure 13a. A 0.003-mole sample of 13a was dissolved in one equivalent of 0.1 *N* hydrochloric acid. After 30 min. bubbles appeared and the solution began to decolorize. After 2 hr. the colorless solution deposited 2-acetylpyrrol, m.p. 91–92°, in quantitative yield.

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Halogenated Aminobenzaldehydes and Aminostyrylquinolines[1]

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Received April 11, 1960

4-(4′-Dimethylaminostyryl)quinolines bearing a halogen atom on the benzene ring of the quinoline portion of the molecule have been prepared from halogen substituted anilines.[2] Additional halogenated styrylquinolines listed in Table I have been prepared, for testing against animal tumors at the Chester Beatty Research Institute. The presence of a bromine atom usually seems to make the compounds less toxic and less active against tumors. Chloride atoms have similar but smaller effect and fluorine atoms have even less effect, but even a fluorine atom in the 2′ position reduces biological activity sharply. The ratio of maximum tolerated dose to minimum effective dose is not necessarily greatest in the most potent compounds and the position of the halogen atom makes a great deal of difference.

EXPERIMENTAL

The 2-chloro-, 2-fluoro-, 3-fluoro-, and 2,5-difluorobenzaldehydes were prepared from the corresponding halodimethylanilines by the method of Campaigne and Archer.[3] 3-Bromo- and 3-chloro-4-dimethylaminobenzaldehyde were prepared by halogenation of 4-dimethylaminobenzaldehyde.[4] Attempts to prepare 3,5-dibromo- and 3-chloro-5-bromodimethylaminobenzaldehyde by treatment of the monohalo compounds with bromine in glacial acetic acid produced crystalline products which seemed to be perbromide hydrobromides of the monohalo compounds. Heating these crystals 3 hr. at 110–130° formed crystalline substances whose composition corresponded to 3,5-dibromo-4-aminobenzaldehyde and 3-chloro-5-bromo-4-aminobenzaldehyde. The loss of the alkyl groups from the dialkylamino group was less surprising in view of Fries[5] report that 2,4,6-tribromo-*N*,*N*-dimethylaniline perbromide hydrobromide on treatment with water in glacial acetic acid formed 2,4,6-tribromo-*N*-monomethylaniline. Molecular models indicate that the crowding of large groups at the amino end of the molecule would produce severe strain, and that even a single bromine or chlorine atom adjacent to the dimethylamino group would cause some strain. It is interesting to note that, although a halogen atom on the benzene ring in the quinoline portion of the styrylquinolines tends to raise the melting point, 4-(4-dimethylamino-3-bromostyryl)quinoline, 4-(4-dimethylamino-3-chlorostyryl)quinoline, and 4-(4-dimethylamino-3-fluorostyryl)quinoline melt approximately 25°, 40°, and 50° lower, respectively, then the unhalogenated parent compound.

3-Bromo- and 3-chlorolepidine, obtained in poor yield by the method of Ellinger,[6] formed styryl derivatives without undue difficulty. In a modification of the Leese method, the picrate was used instead of the hydrochloride, keeping in mind the possible explosive character of the picrate. Numerous efforts to condense 2-chlorolepidine with 4-dimethylaminobenzaldehyde failed, but this base did condense with 4-nitrobenzaldehyde and the resulting nitrocompound was reduced by stannous chloride to 4-(4-aminostyryl)-2-chloroquinoline. 6-Fluorolepidine, b.p. 135° (23 mm.), was prepared from 4-fluoroaniline by William K. Easley, L. Free, and Frank Howell at East Tennessee State College using the method of Campbell and Schaffner.[7] 6-Fluoroquinaldine, m.p. 49.5–51° was provided by Dr. W. F. Little and Mr. Clarence Cook, of the University of North Carolina.

3-Bromo-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared by adding 171 g. (1.07 moles) of bromine in 100 ml. of glacial acetic acid dropwise, with stirring, during 15 min., to 75 g. of 4-dimethylaminobenzaldehyde in 240 ml. of glacial acetic acid, then continuing to stir 45 min. while cooling with an ice bath. The orange crystals were washed well with benzene and dried overnight over sodium hydroxide; yield 216 g., m.p. 128.5–129.3°.

Anal. Calcd. for $C_9H_{10}NOBr.HBr.Br_2$: Oxidizing bromine 34.1%; total bromine 68.18%. Found: Oxidizing bromine 34.19, 34.01; total bromine 68.1, 68.3.[8]

3,5-Dibromo-4-aminobenzaldehyde was prepared by heating 67 g. of the above perbromide 3 hr. at 110–130°. The remaining porous mass was recrystallized from ethanol, from isohexane, and again from ethanol; yield 9.0 g., m.p. 149.5–150.8°; after sublimation m.p. 151.7–152.7°.[10]

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81. Found: C, 30.83; H, 2.10, 1.81.[8]

3-Chloro-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared similarly from 50 g. of 3-chloro-4-dimethylaminobenzaldehyde; yield 66.4 g., m.p. 125.4–127.1°.

Anal. Calcd. for $C_9H_{10}NOCl.HBr.Br_2$: Oxidizing bromine, 37.61; total halogen 64.84. Found: Oxidizing bromine, 36.68, 36.55; total halogen, 63.7, 63.8.[8]

3-Chloro-5-bromo-4-dimethylaminobenzaldehyde was prepared by heating 51.8 g. of the perbromide 8 hr. at 115°,

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