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The Synthesis of Nitro, Amino, and Acetamino Derivatives of 2,3-Dimethylbenzofuran[1]

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Another route to the synthesis of nitro, amino, and acetamino derivatives of 2,3-dimethylbenzofuran was explored. The cyclo-dehydration of 3-(*m*- and *p*-nitrophenoxy)butanones by means of polyphosphoric acid or sulfuric acid afforded 2,3-dimethyl-4- and -5-nitrobenzofurans, which were then converted by reduction to the corresponding 4- and 5-aminobenzofurans. The 4-, 5-, 6-, and 7-aminobenzofurans were prepared by the Hofmann reaction of the corresponding carboxylic amides. The amines thus obtained were converted to 4-, 5-, and 6-acetaminobenzofurans by acetylation. The 5-, 6-,-and 7-acetaminobenzofurans were also prepared by the cyclization of 3-(*p*-, *m*-, and *o*-acetaminophenoxy)butanones. The 7-nitrobenzofuran was prepared by the Sandmeyer reaction of 7-aminobenzofuran. The four aryloxybutanones, 2,3-dimethyl-4- and -7-nitrobenzofurans, 4-amino-2,3-dimethylbenzofuran, and 2,3-dimethyl-4-, -5-, -6-, and -7-benzofurancarboxylic amides are new compounds.

It has previously been reported that the 6-nitro derivative[2] of 2,3-dimethylbenzofuran was prepared by the nitration of the benzofuran, and the 5-nitro derivative[3] was recently prepared by the rearrangement of the *O*-(*p*-nitrophenyl)oxime of butanone, followed by deamino-cyclization, while the 4-, 5-, 6-, and 7-acetamino derivatives[2,4-6] were prepared by the Beckmann rearrangement of oximes of the acetylbenzofurans. The 6-amino derivative[2] was prepared by the reduction of the nitro compound, and the 5-, 6-, and 7-amino

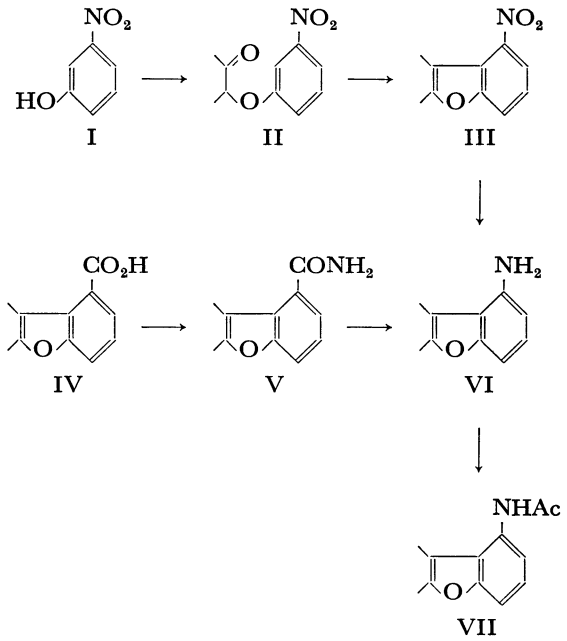

Chart 1

1) The major part of this work was presented at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1969.

2) E. Bisagni, J.-P. Marquet, A. Cheutin, R. Royer, and M.-L. Desvoye, *Bull. Soc. Chim. Fr.*, **1965**, 1466.

3) A. Mooradian, *Tetrahedron Lett.*, **1967**, 407; *cf.* T. Sheradsky, *ibid.*, **1966**, 5225; D. Kaminsky, J. Shavel, Jr., and R. I. Meltzer, *ibid.*, **1967**, 859; A. Mooradian and P. E. Dupont, *ibid.*, **1967**, 2867.

4) E. Bisagni and R. Royer, *Bull. Soc. Chim. Fr.*, **1962**, 925.

5) C. Pène, P. Demerseman, A. Cheutin, and R. Royer, *ibid.*, **1966**, 586.

6) R. Royer, P. Demerseman, C. Pène, and G. Colin, *ibid.*, **1967**, 915.

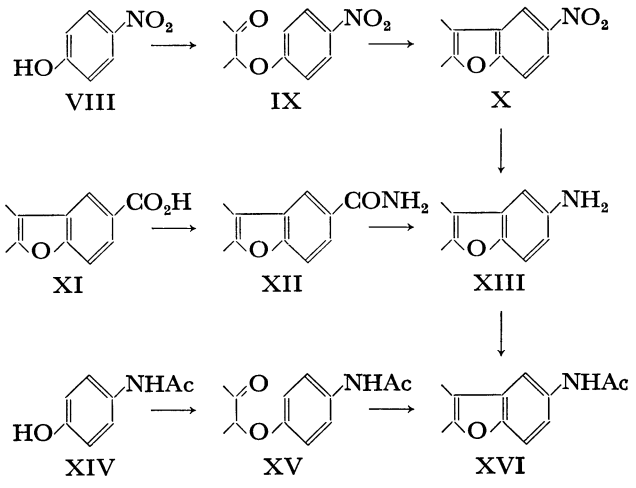

Chart 2

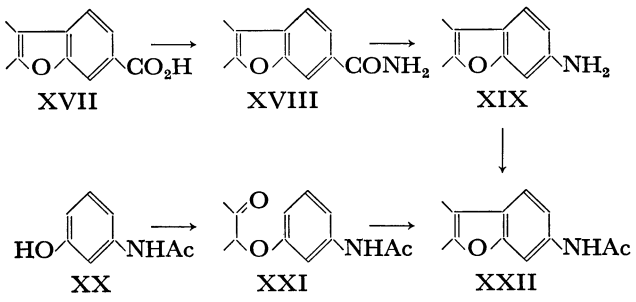

Chart 3

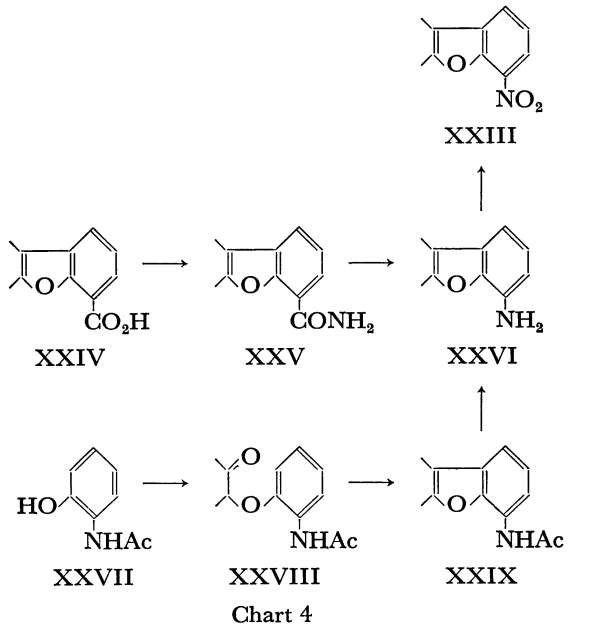

Chart 4

derivatives[4,5] were prepared by the hydrolysis of the acetamino compounds.

In the present paper, the preparation of nitro and acetamino derivatives of 2,3-dimethylbenzofuran by the cyclo-dehydration of 3-(nitro- and acetaminophenoxy)butanones and that of the amino derivatives by the Hofmann reaction of the amides will be described.

The cyclization of 3-(*m*- and *p*-nitrophenoxy)butanones (II and IX) by means of polyphosphoric acid or concentrated sulfuric acid afforded 2,3-dimethyl-4- and -5-nitrobenzofurans (III and X) respectively in good yields. The crude products obtained by the action of polyphosphoric acid on II was found, from a study of its NMR spectrum, to be a mixture of 4- and 6-nitrobenzofurans (97% and 3%); recrystallization afforded a pure compound of 4-nitrobenzofuran (III) (Charts 1 and 2). The analogous cyclization of 3-(*p*-, *m*- and *o*-acetaminophenoxy)butanones (XV, XXI,[7] and XXVIII) with polyphosphoric acid or sulfuric acid afforded 5-, 6-, and 7-acetaminobenzofurans (XVI, XXII, and XXIX) respectively (Charts 2—4). In

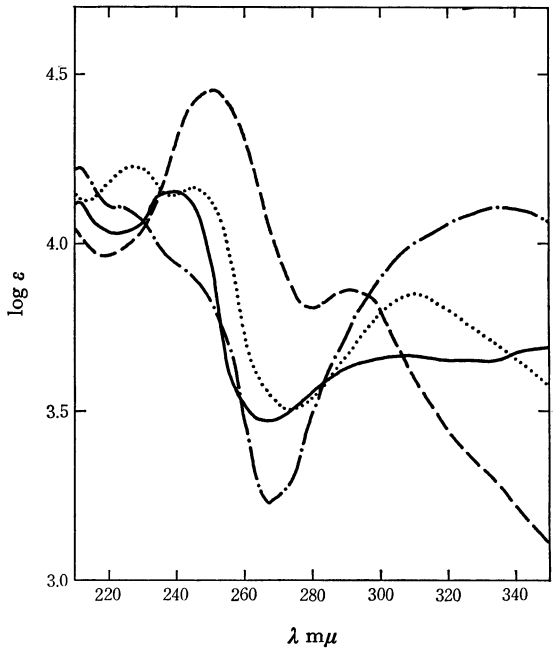

Fig. 1. The UV spectra of nitrobenzofurans:
—— III, —— X, ·–·– 6-nitro-compound, and ····· XXIII.

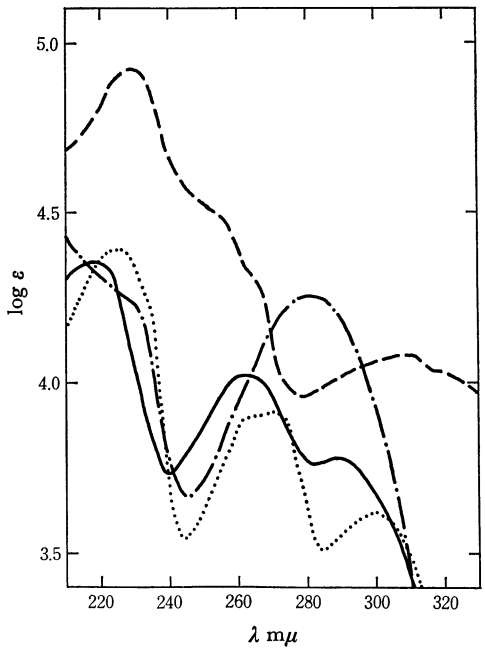

Fig. 2. The UV spectra of acid amides: —— V, —— XII, ·–·– XVIII, and ····· XXV.

7) This compound was obtained only as an impure sample.

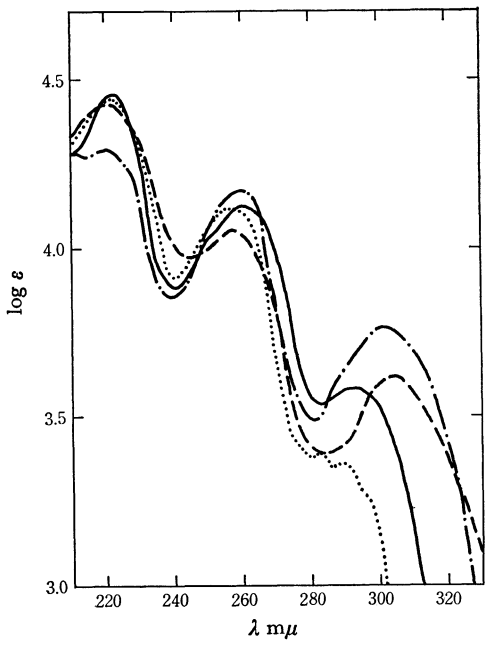

Fig. 3. The UV spectra of aminobenzofurans:
—— VI, —— XIII, -·-·- XIX, and ····· XXVI.

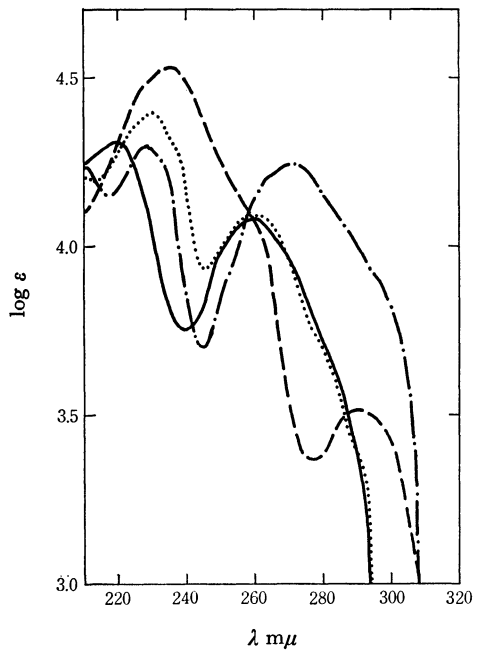

Fig 4. The UV spectra of acetamino compounds:
—— VII, —— XVI, -·-·- XXII, and ····· XXIX.

the case of the cyclization of *m*-substituted aryloxybutanones (II and XXI), it seems notable that the cyclization of II occurred to the *o*-position of the nitro group, while that of XXI occurred to the *p*-position of the acetamino group.[8]

The Hofmann reaction of the amides (V, XII, XVIII, and XXV) of benzofurancarboxylic acids[9,10] (IV, XI, XVII, and XXIV) by the action of sodium hypobromite furnished 4-, 5-, 6-, and 7-amino-2,3-dimethylbenzofurans (VI, XIII, XIX, and XXVI) respectively in low yields (Charts 1—4). The amines VI and XIII were also prepared by the reduction of the corresponding nitrobenzofurans (III and X) with stannous chloride or tin and hydrochloric acid, as has been described in the case of the 6-amino compound[2] XIX, while the acetylation of three amines (VI, XIII, and XIX) with acetic anhydride afforded acetaminobenzofurans (VII, XVI, and XXII). 2,3-Dimethyl-7-nitrobenzofuran (XXIII) was prepared by the Sandmeyer reaction of 7-aminobenzofuran (XXVI) through diazotization and substitution (Chart 4).

It should be mentioned that four aryloxybutanones, II, IX, XV, and XXVIII; two nitrobenzofurans, III and XXIII; the aminobenzofuran VI, and four carboxylic amides, V, XII, XVIII, and XXV, are all new compounds.

In the NMR spectra, the chemical shifts of 3-methyl protons of two 4-substituted benzofurans, III and VI, appeared in a field lower by about 0.1—0.2 ppm than the other isomeric 5-, 6-, and 7-substituted compounds[8] (Table 3).

In the UV spectra, the maximum absorption peaks at 230—250 mμ of 5-nitro-, 5-acetamino-, and 5-carbamoyl-benzofurans have stronger intensities than those of the corresponding 4-, 6-, and 7-substituted isomers. Similarly, 6-nitro-, 6-acetamino-, and 6-carbamoyl-benzofurans showed broader peaks and stronger intensities than those of the 4-, 5-, and 7-substituted ones in the region of 270—335 mμ (Figs. 1—4).

Experimental

All the melting points and boiling points are uncorrected, the NMR spectra were measured on a JEOL JNM-C-60H (60 MHz) spectrometer, and the UV spectra were measured on a Hitachi 139 spectrophotometer. Typical procedures of reactions are described and the detailed data are summarized in the tables.

The Preparation of Aryloxybutanones. Powdered potassium carbonate (168 g) and a small amount (1 g) of potassium iodide were stirred into a solution of *m*-nitrophenol (50 g) and 3-chlorobutanone (47 g) in acetone (400 m*l*), after which the mixture was refluxed for 10 hr. Most of the acetone was distilled off, and the residue was treated with water and extracted with ether. The ethereal solution was concentrated, and the residual product was distilled to give 61 g (81%) of 3-(*m*-nitrophenoxy)butanone (II), bp 154—162°C/6 mmHg. In the case of XXI, it seemed, from the pattern of the IR spectrum, that the product was contaminated by some acetaminobenzofuran (XXII), which was probably formed during distillation.

The Preparation of Nitrobenzofurans. a) By the Cyclization of Aryloxybutanones: *i*) With H_2SO_4: Concentrated sulfuric acid (12.5 g) was stirred, drop by drop, to the aryloxybutanone IX (5 g) below 50°C, after which the mixture was kept at 50°C for 30 min. After cooling, the mixture was poured into ice and extracted with ether. The ethereal solution was concentrated, and the residual product was crystallized from ethanol to give 3.2 g (70%) of 2,3-dimethyl-5-nitrobenzofuran (X), mp 116—117°C.

8) Preliminary report: Y. Kawase, *Chem. Ind.* (London), **1970**, 687.
9) Y. Kawase and M. Takashima, This Bulletin, **40**, 1224 (1967).
10) Y. Kawase, T. Okada, and T. Miwa, *ibid.*, **43**, 2884 (1970).

ii) With Polyphosphoric Acid (PPA): A mixture of the aryloxybutanone IX (10 g) and PPA (n=2.5,[11] 200 g) was heated at 100°C for 1.5 hr while being stirred. The resulting mixture was treated as has been described above to give

TABLE 1. REACTION CONDITIONS AND THE RESULTS

Starting compound	Reagent	Product	Mp°C (solvent[a]) or bp°C/mmHg	Yield %
	Preparation of Aryloxybutanones			
I	Cl-butanone	II	154—162/6	81
VIII	Cl-butanone	IX	66—67(Et)	72.5
XIV	Cl-butanone	XV	112—113(Et)	68
XX	Cl-butanone	XXI[b]	245—255/17	60
XXVII	Cl-butanone	XXVIII	188—193/6	73
	Cyclo-dehydration of Aryloxybutanones			
II	H_2SO_4	III	80.5—81(Et)	27
II	PPA[c]	III	80.5—81(Et)	46[d]
IX	H_2SO_4	X	116—117[e](Et)	70
IX	PPA	X	116—117[e](Et)	73
XV	H_2SO_4	XVI	174—174.5[f](Et)	55
XV	PPA	XVI	174—174.5[f](Et)	80
XXI[b]	PPA	XXII	181—181.5[g](Et)	55
XXVIII	H_2SO_4	XXIX	134—135.5[h](Et)	29
	Amines from Nitro Compounds			
III	$SnCl_2$-HCl	VI	41—43(Pe)	59
III	Sn-HCl	VI	41—43(Pe)	21.5
X	$SnCl_2$-HCl	XIII	81.5—83[i](Pe)	80
X	Sn-HCl	XIII	81.5—83[i](Pe)	38
	Acid Amides from Acids			
IV	$SOCl_2$-NH_4OH	V	192.5—194(Et)	66.5
XI	$SOCl_2$-NH_4OH	XII	162.5—163(Et)	50
XVII	$SOCl_2$-NH_4OH	XVIII	175—176(Et)	42
XXIV	$SOCl_2$-NH_4OH	XXV	188—189.5(Et)	59
	Amines from Acid Amides			
V	NaOBr	VI	41—43(Pe)	29
XII	NaOBr	XIII	81.5—83[i](Pe)	38
XVIII	NaOBr	XIX	58—58.5[j](Pe)	17
XXV	NaOBr	XXVI	62—63[k](Pe)	25
	Acetamino Compounds from Amines			
VI	Ac_2O-Py	VII	177.5—178[l](Et)	23
XIII	Ac_2O-Py	XVI	174—174.5[f](Et)	31
XIX	Ac_2O-Py	XXII	181—181.5[g](Et)	79.5
	Nitro Compound from Amine			
XXVI	Sandmeyer reaction	XXIII	76.5—77(Et)	4

a) Et: ethanol, Pe: Petroleum ether. b) The crude product. c) Polyphosphoric acid. d) The crude product, mp 73—74°C, 67% yield, contains a 3% of the isomeric 6-nitro compound. e) Mp is not given in the Ref. 3. f) Lit. mp 174—175°C (Ref. 2). g) Lit. mp 182—183°C (Ref. 4). h) Lit. mp 126°C (Ref. 5). i) Lit. mp 79°C (Ref. 2). j) Lit. mp 54°C (Ref. 4). k) Lit. mp 62.5°C (Ref. 5). l) Lit. mp 176°C (Ref. 6).

11) Prepared from phosphoric acid (85%) and phosphorus pentoxide (1. 1: 1).

TABLE 2. THE ANALYSES OF NEW COMPOUNDS

Compd	Formula	Found C%	Found H%	Found N%	Calcd C%	Calcd H%	Calcd N%
	Aryloxybutanones						
II	$C_{10}H_{11}O_4N$	57.92	5.14	6.50	57.41	5.30	6.70
IX	$C_{10}H_{11}O_4N$	57.14	5.08	6.64	57.41	5.30	6.70
XV	$C_{12}H_{15}O_3N$	65.56	7.18	6.17	65.14	6.83	6.33
XXVIII	$C_{12}H_{15}O_3N$	65.23	6.75	6.33	65.14	6.83	6.33
	Nitro Compounds						
III	$C_{10}H_9O_3N$	63.01	4.64	7.04	62.82	4.75	7.33
XXIII	$C_{10}H_9O_3N$	62.79	4.63	7.28	62.82	4.75	7.33
	Amino Compound						
VI	$C_{10}H_{11}ON$	74.51	6.98	8.71	74.51	6.88	8.69
	Acid Amides						
V	$C_{11}H_{11}O_2N$	69.19	5.78	7.18	69.82	5.86	7.40
XII	$C_{11}H_{11}O_2N$	69.61	5.99	7.18	69.82	5.86	7.40
XVIII	$C_{11}H_{11}O_2N$	69.54	5.97	7.17	69.82	5.86	7.40
XXV	$C_{11}H_{11}O_2N$	69.57	5.83	7.39	69.82	5.86	7.40

TABLE 3. THE NMR SPECTRA OF NITRO- AND AMINO-BENZOFURANS[a]

Compd	NH_2	2-Me	3-Me
III		2.46	2.27
X		2.41	2.19
b)		2.44	2.18
XXIII		2.47	2.17
VI	3.69	2.27	2.27
XIII	3.33	2.31	2.05
XIX	3.34	2.27	2.04
XXVI	3.66	2.32	2.07

a) δ-Values (ppm) measured in CCl_4 (*ca.* 5% solution), using TMS as an internal standard.
b) 2,3-Dimethyl-6-nitrobenzofuran.

6.65 g of the nitrobenzofuran X, mp 116—117°C. In the case of the cyclization of II, 6.2 g of a crude product, mp 73—74°C, was obtained after one crystallization. It was found, from the NMR spectrum, to be a mixture of 2,3-dimethyl-4- and -6-nitrobenzofurans; the percentage composition was determined by estimating the areas of the peaks corresponding to the 3-methyl protons (see Table 1). Further recrystallization furnished 4.25 g (46%) of the pure III, mp 80.5—81°C.

b) By the Sandmeyer Reaction: According to the usual manner,[12] the amine XXVI (1.4 g) was diazotized in acetic acid (16 m*l*) with sodium nitrite (1.6 g) and sulfuric acid (8 m*l*); the diazonium compound thus formed was treated with a decomposition mixture which had been prepared from copper sulfate (8 g), sodium sulfite (8 g), and sodium nitrite (20%, 8 g). The product was crystallized from ethanol to give 65 mg (4%) of 2,3-dimethyl-7-nitrobenzofuran (XXIII), mp 76.5—77°C.

The Preparation of Acid Amides. A mixture of 2,3-dimethyl-4-benzofurancarboxylic acid[9] (IV) (4 g) and thionyl chloride (10 g) was refluxed for 1 hr. The excessive reagent was then distilled off, and the residual product was dissolved in dioxane (10 m*l*). A concentrated aqueous ammonia solution (20 m*l*) was added to the solution, and the mixture was treated with water after it had stand for 1 hr. The crystalline

12) H. H. Hodgson, A. P. Mahadevan, and E. R. Ward, "Organic Syntheses," Coll. Vol. 3 (1955), p. 341.

product thus formed was collected and recrystallized from ethanol to give 2.6 g (65.5%) of the acid amide V, mp 192.5—194°C.

The Preparation of Aminobenzofurans. *a) By the Reduction of Nitrobenzofurans*: *i*) With $SnCl_2$-HCl: A mixture of the nitrobenzofuran III (5 g), stannous chloride (20 g), and concentrated hydrochloric acid (20 m*l*) was refluxed for 1 hr. An aqueous sodium hydroxide solution (27%, 123 g) was added to the mixture with cooling, and then the mixture was extracted with ether. The ethereal solution was concentrated; the residual product was distilled at 150—164°C/20 mmHg and then crystallized from petroleum ether to give 2.5 g (59%) of 4-amino-2,3-dimethylbenzofuran (VI), mp 41—43°C.

ii) With Sn-HCl: Concentrated hydrochloric acid (5 m*l*) was stirred into a mixture of the nitrobenzofuran III (1.1 g), ethanol (15 m*l*), and tin (1.4 g), after which the mixture was heated at 45°C for 3 hr while being stirred. After cooling, the mixture was treated as has been described in *i*) to give 0.2 g (21.5%) of the amine VI, mp 41—43°C.

b) By the Hofmann Reaction: A solution of the amide V (2 g) in dioxane (40 m*l*) was stirred into an aqueous sodium hypobromite solution which had been prepared from bromine (2.7 g), sodium hydroxide (4.5 g), water (27 m*l*), and ice (27 g). The mixture was heated at 70°C for 1 hr while being stirred. After the addition of an aqueous sodium hydroxide solution (50%, 13 g), the mixture was heated at 80°C for another hour with stirring and then cooled. The mixture was treated with water and extracted with ether. On treatment as in *a-i*, the ethereal solution gave the amine VI.

The identity of XIII, XIX, and XXVI with the authentic samples prepared independently[2,4,5] was confirmed by a mixed-melting-point determination and by a comparison of their IR spectra.

The Preparation of Acetaminobenzofurans. *a) By the Cyclization of Aryloxybutanones*: Two aryloxybutanones, XV and XXVIII, were treated with sulfuric acid at 40°C to give 5- and 7-acetaminobenzofurans (XVI and XXIX), and XV and crude XXI were treated with PPA to give XVI and 6-acetaminobenzofuran (XXII), as has been described for the nitro compounds.

b) By the Acetylation of Amines: Three amines, VI, XIII, and XIX, were acetylated by the acetic anhydride-pyridine method to give 4-acetaminobenzofuran (VII), XVI, and XXII.

Compounds VII, XVI, XXII, and XXIX were identified by a mixed-melting-point determination and by a comparison of the IR spectra with those of authentic samples.[2,4-6]

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