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The Acetylation of Acetamino-2,3-dimethylbenzofurans and the Synthesis of Furoquinolines*1

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The acetylation of 2,3-dimethylbenzofuran derivatives has previously been reported in the cases of alkyl,[1–3] methoxyl,[4] hydroxyl,[5] halo,[6] acetyl,[7–9] and methoxycarbonyl[9] compounds. In the cases of the methoxyl, hydroxyl, and acetyl compounds, the acetylation occurred at the position under the influence of the substituent; it occurred at the 6-position under the influence of the furan ring in the cases of the methoxycarbonyl compounds, while it occurred at various positions in the cases of the alkyl compounds. It has also been reported that the nitration of the 5-acetamino-2,3-dimethyl-

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

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

2) R. Royer, M. Hubert-Habart, L. René and A. Cheutin, *ibid.*, **1964**, 1259.

3) Y. Kawase, R. Royer, M. Hubert-Habart, A. Cheutin, L. René and J.-P. Buisson, *ibid.*, **1964**, 3131.

4) R. Royer, E. Bisagni, A.-M. Laval-Jeantet and J.-P. Marquet, *ibid.*, **1965**, 2607.

5) Y. Kawase, M. Nanbu and F. Miyoshi, This Bulletin, **41**, 2676 (1968).

6) C. Goldenberg, F. Binon and C. Gillyus, *Chim. Ther.*, **1966**, 221.

7) Y. Kawase, M. Hubert-Habart, J.-P. Buisson and R. Royer, *Compt. Rend.*, **258**, 5007 (1964).

8) R. Royer, Y. Kawase, M. Hubert-Habart, L. René and A. Cheutin, *Bull. Soc. Chim. Fr.*, **1966**, 211.

9) Y. Kawase and M. Takashima, This Bulletin, **40**, 1224 (1967).

benzofuran afforded the 6-nitro derivative.[10]

Now, in the present experiments, the Friedel-Crafts acetylation of 4-, 5-, 6-, and 7-acetamino-2,3-dimethylbenzofurans[11] (**1**, **4**, **8**, and **12**) was carried out. The acetylated products (**2**, **5**, **9**, and **13**) obtained were hydrolyzed to the corresponding amino-ketones (**3**, **6**, **10**, and **14**), the structures of which were determined by the NMR data (see Table 2) and by converting the amino-ketones (**6**, **10**, and **14**) to the known 2,3-dimethyl-6- and -4-acetylbenzofurans (**7** and **11**) (see Chart 1). The coupling constants and δ-values in the NMR spectra indicate that **3** and **10** have aromatic *meta* protons, that **6** has *para* protons, and that **14** has *ortho* protons.

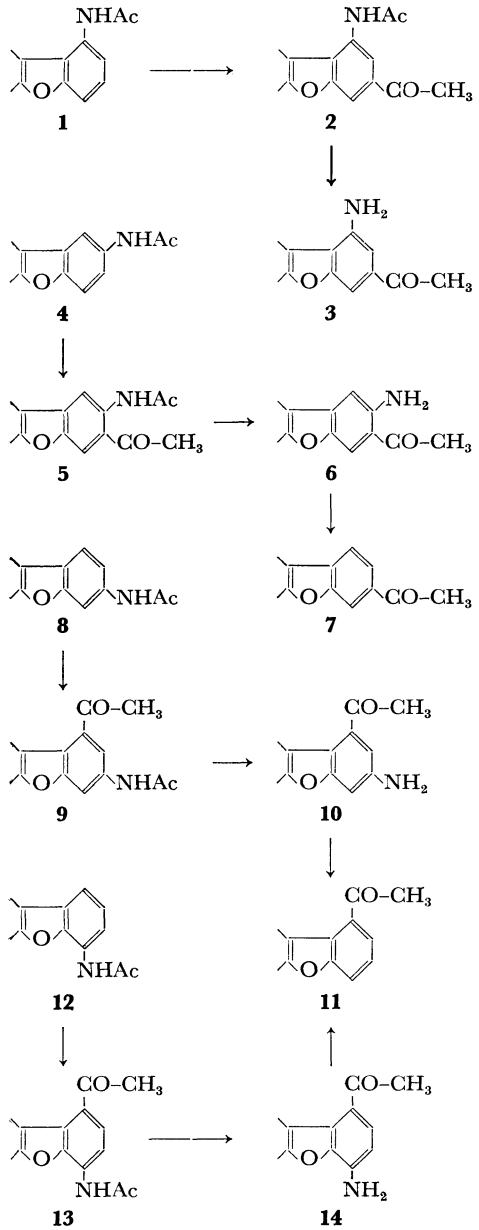

Chart 1

In conclusion, it may be considered that, in the electrophilic substitution, every position on the benzene ring of 2,3-dimethylbenzofuran, especially the 6-position, are activated by the furan ring, and that the acetylation of the compound **4** occurred at the 6-position, which is activated by both the furan ring and the acetamino group, while the compound **1** was acetylated at the 6-position, which is activated by the furan ring. Further, the compound **8** was acetylated at the 4-position, which seems to be fairly well activated by the furan ring, and the compound **12** was acetylated at the 4-position, which is activated by both the acetamino group and the furan ring.

Acetamino-ketone (**5**) was heated with an aqueous sodium hydroxide solution in ethanol to give a compound the structure of which was considered to be 2,3,8-trimethylfuro[2,3-*g*]-6(5*H*)-quinolone (**15**) on the basis of the data of elemental analysis and UV spectrum and on the basis of the analogous formation of 4-methyl-2(1*H*)-quinolone[12] by a similar reaction of *o*-acetaminophenyl methyl ketone (**17**). The treatment of **5** with polyphosphoric acid afforded a compound the structure of which was considered to be 6-(5-acetamino-2,3-dimethyl-6-benzofuranyl)-2,3,8-trimethylfuro[2,3-*g*]quinoline (**16**) on the basis of the data of elemental analysis and UV spectrum and on the basis of the analogous formation of 2-(*o*-acetaminophenyl)-4-methylquinoline (**18**) by a similar reaction of the acetamino-ketone (**17**). The quinoline (**18**) was also obtained by the acetylation of the corresponding amine (**20**), while the compounds **18** and **20** have been prepared by Camps[12] by the action of sodium hydroxide on **17** and amino-ketone (**19**) respectively. The quinoline (**16**) was also obtained in a low yield by the use of acetic acid and polyphosphoric acid on the acetaminobenzofuran (**4**) (see Chart 2).

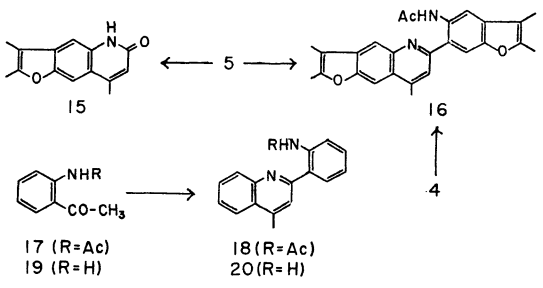

Chart 2

10) C. Pène, P. Demerseman, A. Cheutin and R. Royer, *Bull. Soc. Chim. Fr.*, **1966**, 586.

11) Y. Kawase, S. Takata and E. Hikishima, This Bulletin, to be published.

12) R. Camps, *Ber.*, **32**, 3230 (1899); *Arch. Pharm.*, **237**, 670 (1899).

Table 1. The MP and analyses of the new compounds

Compd.	Mp (°C)[a]	Formula	Found (%)			Calcd (%)		
			C	H	N	C	H	N
		Acetamino-ketones						
2	181—182	$C_{14}H_{15}O_3N$	68.32	6.03	5.73	68.55	6.16	5.71
5	181.5—182	$C_{14}H_{15}O_3N$	68.47	6.24	5.75	68.55	6.16	5.71
9	180—181	$C_{14}H_{15}O_3N$	68.62	6.17	5.61	68.55	6.16	5.71
13	169—171	$C_{14}H_{15}O_3N$	68.35	6.21	5.78	68.55	6.16	5.71
		Amino-ketones						
3	138—140	$C_{12}H_{13}O_2N$	70.66	6.28	6.67	70.91	6.45	6.89
6	144—145.5	$C_{12}H_{13}O_2N$	70.98	6.20	6.65	70.91	6.45	6.89
10	114.5—115.5	$C_{12}H_{13}O_2N$	70.93	6.46	6.62	70.91	6.45	6.89
14	142—143	$C_{12}H_{13}O_2N$	71.19	6.27	6.64	70.91	6.45	6.89
		Furoquinolines						
15	318—319 (dec.)	$C_{14}H_{13}O_2N$	73.93	5.63	6.06	73.99	5.77	6.16
16	298	$C_{26}H_{24}O_3N_2$	75.84	5.79	6.68	75.70	5.89	6.79

a) From ethanol.

Experimental

All the melting points are uncorrected; the NMR spectra were measured on a JEOL Model JNM-C-60H (60 MHz) spectrometer, while the UV spectra were measured on a Hitachi Model 139 spectrophotometer. The melting points and elemental analyses are summarized in Table 1.

Acetylation of Acetaminobenzofurans. *a) By AcCl-$AlCl_3$.* Powdered aluminum chloride (1.3 g) was stirred into a mixture of **1**[11] (1 g), acetyl chloride (0.45 g), and carbon disulfide (20 m*l*); the new mixture was stirred for 3 hr at room temperature and then allowed to stand overnight. The mixture was poured into dilute hydrochloric acid and extracted with chloroform. The organic layer was washed with an aqueous sodium hydroxide solution. The residual product from the organic layer was crystallized from ethanol to give 4-acetamino-2,3-dimethyl-6-benzofuranyl methyl ketone (**2**); mp 181—182°C; 0.25 g (21%). Similarly, 5-acetamino-2,3-dimethyl-6-benzofuranyl methyl ketone (**5**) and 6- and 7-acetamino-2,3-dimethyl-4-benzofuranyl methyl ketones (**9** and **13**) were also obtained from acetaminobenzofurans (**4**, **8**, and **12**) in yields of 50, 58, and 20% respectively.

b) By Ac_2O-$AlCl_3$. Aluminum chloride (2.6 g) was added to a mixture of **1** (1 g), acetic anhydride (0.5 g), and carbon disulfide (20 m*l*), and the mixture was treated much as has been described in a) to give **2** in a yield of 50%. The other acetamino-ketones (**5**, **9**, and **13**) were also obtained in yields of 76, 71, and 35%.

Hydrolysis of the Acetamino-ketones. The acetamino-ketones (**2**, **5**, **9**, and **13**) were hydrolyzed by refluxing them for 1 hr with dilute hydrochloric acid in ethanol to give the corresponding 4- and 5-amino-2,3-dimethyl-6-benzofuranyl methyl ketones (**3** and **6**) and 6- and 7-amino-2,3-dimethyl-4-benzofuranyl methyl ketones (**10** and **14**) in yields of 41, 90, 85, and 41% respectively.

Deamination of the Amino-ketones. The amino-ketones (**6**, **10**, and **14**) were diazotized and then decomposed in the presence of copper powder by the usual procedure[13] to give 6-[1] and 4-benzofuranyl methyl ketones[9] (**7** and **11**) in yields of 57, 73, and 42% respectively.

Table 2. The NMR spectra of the amino-ketones[a]

Compd.	Ph-H[b]		NH_2	COMe	2-Me	3-Me
3	7-H	5-H	3.93	2.55	2.33	2.33
	7.43(d)	7.03(d)				
	J=2 Hz					
6	7-H	4-H	5.73	2.58	2.31	2.02
	7.58	6.48				
10	5-H	7-H	3.67	2.56	2.31	2.11
	6.83(d)	6.78(d)				
	J=2 Hz					
14	5-H	6-H	4.02	2.58	2.39	2.29
	7.42(d)	6.47(d)				
	J=8 Hz					

a) δ (ppm) values measured in $CDCl_3$ (*ca.* 5% solution), with TMS as the internal standard.
b) d: Doublet.

2,3,8-Trimethylfuro[2,3-*g*]-6(5*H*)-quinolone (15). An aqueous sodium hydroxide solution (30%, 16 m*l*) was added, drop by drop, to a hot solution of **5** (2 g) in ethanol (80 m*l*), after which the mixture was refluxed for 5 hr. Most of the ethanol was then distilled off, and the residue was steam-distillated. The residual crystalline precipitates were recrystallized from ethanol to give the furoquinolone (**15**); mp 318—319°C; 1.55 g (84%); λ_{max}^{EtOH} mμ (log ε): 227 (4.66), 252 (4.03), 322 (4.29), and 342 (4.23).

6-(5-Acetamino-2,3-dimethylbenzofuranyl)-2,3,8-trimethylfuro[2,3-*g*]quinoline (16). *a) From the*

13) *Cf.* L. A. Bigelow, J. R. Johnson and L. T. Sandborn, "Organic Syntheses," Coll. Vol. 1, p. 133 (1956).

Acetamino-ketone (**5**). A mixture of **5** (2 g) and polyphosphoric acid (n=2.5, 40 g) was heated at 100°C for 1 hr. The cooled mixture was poured into ice water and extracted with ethyl acetate, and the residual product from the organic layer was crystallized from ethyl acetate or benzene to give **16**; mp 298°C; 1.37 g (81%); λ_{max}^{EtOH} mμ (log ε): 258 (4.34), 304.5 (4.34), and 363 (4.05).

b) From the Acetaminobenzofuran (**4**). A mixture of **4** (1 g), acetic acid (0.45 g), and polyphosphoric acid n=1.5, 20 g) was heated at 100°C for 1 hr. The cooled mixture was then treated much as has been described in a) to give **16** (mp 290°C; 0.05 g (5%)), which was identical with the above sample.

2-(2-Acetaminophenyl)-4-methylquinoline (18). *a) From Acetamino-ketone* (**17**). The compound **17** (2 g) was treated with polyphosphoric acid (n=2.5, 40 g), much as has been described in the case of **16**, to give **18**; mp 138.5—139°C (lit,[12] mp 138°C); 1.2 g(77%); λ_{max}^{EtOH} mμ (log ε): 244 (4.40), 259.5 (4.21), and 338 (3.74).

b) By Acetylation of Amine (20). The amine **20**[12] (0.09 g) was acetylated with acetic anhydride - acetic acid to give **18**, mp 134—136°C; 0.05 g (47%), which was identical with the above sample.

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