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Reaction of 2-Aminobenzophenones with Aliphatic Acids in the Presence of Polyphosphoric Acid*1

Takumi ISHIWAKA, Mitsuo YONEMOTO, Kakuzo ISAGAWA and Yasaburo FUSHIZAKI

Department of Applied Chemistry, Faculty of Engineering, University of Osaka Prefecture, Sakai, Osaka

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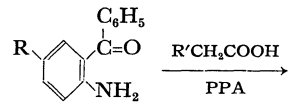
The reaction of 2-aminobenzophenones with aliphatic acids, such as acetic acid, propionic acid, *n*-butyric acid, and bromoacetic acid, in the presence of polyphosphoric acid afforded 6-substituted 2-anilino-4-phenylquinoline derivatives in fairly good yields. Some of these quinolines were acetylated in the usual way, and the products, 2-(*N*-acetylanilino)quinolines, were treated with sodium ethoxide to give 1-quinolyl-2(1*H*)-quinolone derivatives. 2-Amino-5-chlorobenzophenone (Ic) reacted with an equimolar amount of 2-acetamido-5-methylbenzophenone to give 2-(2-benzoyl-4-methylanilino)-6-chloro-4-phenylquinoline, which was also obtained from the reaction of 2,6-dichloro-4-phenylquinoline with Ib in the presence of copper powder. It was found that the reaction mechanism in the formation of 2-anilinoquinolines is similar in type to that in Friedländer's reaction. Furthermore, the structures of the 2-anilinoquinolines are discussed on the basis of our NMR spectral study.

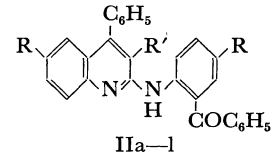
In an earlier paper,[1] 2-aminobenzophenones (I) were treated with zinc chloride to afford the rearrangment products, benzanilides, together with dibenzo-[*b*,*f*]-1,5-diazocines and 9-acridones. On the other hand, it has been reported by Dippy *et al.*[2,3] that, on the treatment of *N*-monoacyl- or *N*,*N*-diacylaniline with anhydrous aluminum chloride or zinc chloride, a migration of their acyl groups occurred.

Then, 2-acetamido-5-chlorobenzophenone (IIIc), which has two acyl groups, was treated with zinc chloride at 190—200°C for 10 hr as the basis for a discussion of the rearrangement of the acyl groups. However, this reaction gave no rearrangement products. It did, though, afford intermolecular condensation product, 2-(2-benzoyl-4-chroroanilino)-6-chloro-4-phenylquinoline (IIc), in a 54% yield; it had already prepared in a 90% yield by Drukker and Judd[4] by the treatment of IIIc with polyphosphoric acid (PPA) at 130—140°C for 2 hr. The present authors found that this compound could easily be obained by slightly modifying Drukker's method.

Now, this paper will report the direct syntheses of 2-anilinoquinolines (II) from I and the syntheses of 1-quinolyl-2(1*H*)-quinolones (IX), and will des-



Ia : R=H
b : R=CH_3
c : R=Cl



IIa—l

IIa—l: R and R′ are shown in Table 1

Scheme 1

*1 Part VIII, "*o*-Aminobenzophenone Derivatives." This study was presented at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1969. Part VII: T. Ishiwaka, M. Sano, K. Isagawa and Y. Fushizaki, This Bulletin, **43**, 135 (1970).

1) K. Isagawa, T. Ishiwaka, M. Kawai (the late) and Y. Fushizaki, This Bulletin, **42**, 2066 (1969).

2) J. F. J. Dippy and J. H. Wood, *J. Chem. Soc.*, **1949**, 2719.

3) J. F. J. Dippy and V. Moss, *ibid.*, **1952**, 2205.

4) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **3**, 359 (1966); *Chem. Abstr.*, **65**, 20096 (1966).

Table 1. 2-Anilinoquinolines (II)

Compound II	R	R′	Reaction conditions Temp. °C	Time min	Yield %	Mp °C	Elementary analysis (%) Calcd C	H	N	Found C	H	N
a	H	H	140—145	30	80	140—142	83.98	4.96	6.93	84.22	5.03	7.00
b	CH_3	H	150—155	20	72	179—181	84.08	5.65	6.54	84.32	5.81	6.83
c	Cl	H	140—145	15	89	188—190	71.65	3.87	5.97	71.80	4.04	5.97
d	H	CH_3	110—115	10	90	191—192	84.03	5.35	6.76	84.25	5.56	7.05
e	CH_3	CH_3	125—130	15	91	194—196	84.13	5.92	6.33	84.03	6.20	6.60
f	Cl	CH_3	125—130	15	94	222—224	72.06	4.17	5.80	72.03	4.40	5.77
g	H	C_2H_5	110—115	15	85	162—164	84.09	5.66	6.54	83.79	5.71	6.50
h	CH_3	C_2H_5	110—115	15	81	216—218	84.18	6.18	6.14	84.45	6.30	6.04
i	Cl	C_2H_5	110—115	15	92	229—230	72.44	4.46	5.63	72.68	4.46	5.78
j	H	Br	105—110	15	71	210—211	70.16	4.00	5.84	70.35	4.07	5.61
k	CH_3	Br	105—110	15	72	216—217	71.01	4.57	5.52	71.30	4.62	5.56
l	Cl	Br	105—110	15	82	228—230	61.33	3.13	5.11	61.62	3.31	5.20
m[a]			135—140	30	83	191—192	77.58	4.71	6.24	77.44	4.95	6.18
n[a]			155—160	60	94	183—185	77.58	4.71	6.24	77.40	4.66	6.14
n[b]			175—180	300	24							

Compound II	R	R′	NMR[c] δ(ppm) NH	Arom H	R′	R
a	H	H	11.08(b)	9.43—7.08(m)	6.96(s)	—
b	CH_3	H	10.74(b)	9.24—7.21(m)	6.89(s)	2.40(s), 2.28(s)
c	Cl	H	10.90(b)	9.38—7.28(m)	6.95(s)	—
d	H	CH_3	11.14(b)	9.50—6.82(m)	2.32(s)	—
e	CH_3	CH_3	10.95(b)	9.48—6.98(m)	2.30(s)	2.30(s), 2.30(s)
f	Cl	CH_3	11.02(b)	9.43—7.18(m)	2.28(s)	—
g	H	C_2H_5	11.28(b)	9.64—7.06(m)	2.78(q), 1.26(t)	—
h	CH_3	C_2H_5	11.09(b)	9.40—6.94(m)	2.74(q), 1.23(t)	2.33(s), 2.33(s)
i	Cl	C_2H_5	11.10(b)	9.52—7.12(m)	2.74(q), 1.23(t)	—
j	H	Br	11.34(b)	9.47—7.00(m)	—	—
k	CH_3	Br	11.16(b)	9.22—7.00(m)	—	2.35(s), 2.35(s)
l	Cl	Br	11.21(b)	9.33—7.22(m)	—	—
m[a]			10.88(b)	9.40—7.30(m)	6.88(s)	2.41(s)
n[a]			10.86(b)	9.20—7.33(m)	6.90(s)	2.28(s)
n[b]						

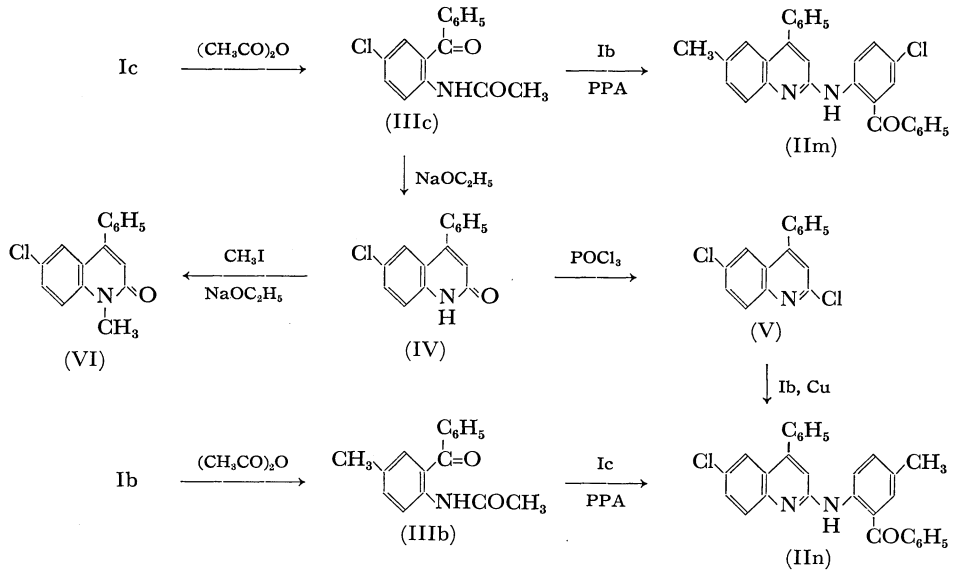
a) From the reactions of Ib with IIIc and of Ic with IIIb.
b) From the reaction of Ib with V in the presence of copper powder.
c) Measured in $CDCl_3$, using tetramethylsilane as the internal standard. b: broad, m: multiplet, s: singlet, t: triplet, q: quartet.

cribe the reaction mechanism in the formation of II.

When I was reacted with various aliphatic acids in the presence of PPA at the temperature shown in Table 1 for 10—30 min, the corresponding 2-anilinoquinolines were obtained in fairly good yields. By using this method, the reaction time could be very much shortened (Scheme 1).

The yields, physical properties, and results of the elemental analyses of II are summarized in Table 1.

In order to discuss the reaction mechanism in the formation of II, the reaction of 2-acetamido-5-chlorobenzophenone (IIIc) with Ib and that of 2-acetamido-5-methylbenzophenone (IIIb) with Ic were carried out in the presence of PPA. 2-(2-Benzoyl-4-chloroanilino)-6-methyl-4-phenylquinoline (IIm) was formed from the former reaction. On the other hand, the latter reaction afforded 2-(2-benzoyl-4-methylanilino)-6-chloro-4-phenylquinoline (IIn), which was also obtained from the reaction of 2,6-dichloro-4-phenylquinoline (V) with Ib, using copper powder as the catalyst. The formations of IIn in the former reaction and of IIm in the latter reaction were not detected (Scheme 2).



Scheme 2

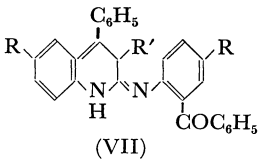
It may be suggested from these facts that this reaction involves the preliminary acylation of I by aliphatic acids to give 2-acylaminobenzophenone derivatives, which subsequently react with other 2-aminobenzophenones in a manner presumably analogous to the mechanism of the Friedländer process.

In the case of the reaction described by Drukker and Judd, Kanaoka[5] has suggested that Ic, resulting from the deacylation of IIIc, condensed with other IIIc to give IIc. Although he has not described the mechanism of this condensation in detail, it is probably analogous to that of the Friedländer process.

Drukker and Judd have reported that, in the NMR spectrum*2 of IIc, the sharp peak at δ 6.86 ppm is due to NH (1H). On treatment with deuterium oxide, however, this peak remains and the broad peak at δ 10.90 ppm (1H) disappears. As is shown in Table 1, the other 3-nonsubstituted anilinoquinolines, such as IIa, IIb, IIm, and IIn, also reveal peaks at δ 6.88—6.96 ppm, while the 3-substituted compounds, IId—IIl, show no peaks in this range.

The above observations indicate that the peaks at δ 6.96 ppm and at δ 10.90 ppm in IIc are to be assigned to CH at the 3-position and to NH respectively.

On the other hand, the methine-proton signals at the 3-position of 6-chloro-4-phenyl-2(1*H*)-quinolone (IV)*3 and its 1-methyl derivative (VI)*2 appear at δ 6.56 ppm and at δ 6.76 ppm respectively.



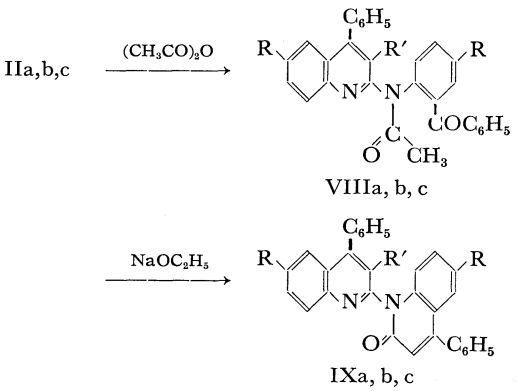
(VII)

Fig. 1

The complex multiplets at δ 7.44—7.86 ppm and at δ 7.43—7.73 ppm in them correspond to aromatic proton signals. In the case of 2,6-dichloro-4-phenylquinoline (V),*2 however, there is only the peak of the aromatic proton at δ 7.48—8.14 ppm (multiplet), not the peak of methine-proton at δ 6.5—6.9 ppm.

The differences may be successfully explained in terms of the non-aromaticity of the methine-protons in IV and VI, and the aromaticity in V.

Considering the above observations, it may be



a: R=R′=H b: R=CH3, R′=H c: R=Cl, R′=H

Scheme 3

5) Y. Kanaoka, *Kagaku*, Vol. 24, No. 3, Kagaku Dojin, Kyoto (1969), p. 42.

*2 Measured in $CDCl_3$.

*3 Measured in $CDCl_3$–DMSO-d_6 (3 : 2).

Table 2. 2-(*N*-Acetylanilino)quinolines and 1-quinolyl-2(1*H*)-quinolones

Compound		Yield %	Mp °C	Elementary analysis (%) Calcd C	H	N	Found C	H	N	NMR[c] δ (ppm) Arom H	CH[d]	CH_3
VIII[a]	a	72	146—147	81.43	5.01	6.33	81.13	4.85	6.14	7.84—7.36(m)	—	2.20(s)
	b	91	173—174	81.68	5.57	5.95	81.43	5.87	5.77	7.89—7.30(m)	—	2.40(s), 2.40(s), 2.17(s)
	c	94	187—188	70.46	3.94	5.48	70.47	3.64	5.19	7.80—7.39(m)	—	2.19(s)
IX[b]	a	87	290	84.88	4.75	6.60	84.63	4.66	6.42	8.30—7.26(m)	6.75(s)	—
	b	79	196—198	84.93	5.35	6.19	84.84	5.54	6.14	8.18—7.27(m)	6.72(s)	2.52(s), 2.28(s)
	c	86	251—252	73.03	3.68	5.68	73.21	3.39	5.67	8.22—7.32(m)	6.77(s)	—

a) Reaction conditions: temp. 75—80°C, time 60 min.
b) Reaction conditions: temp. 75—80°C, time 30 min.
c) Measured in $CDCl_3$, using tetramethylsilane as the internal standard. m:multiplet, s: singlet.
d) Methine-proton at 3-position of quinoline ring or quinolone ring.

deduced that the 2-anilinoquinolines II exist as imino-type VII, as is shown in Fig. 1.

6-Substituted 2-(4-substituted *N*-acetylanilino)-4-phenylquinolines (VIII) which had been obtained by the acetylation of the quinolines II with acetic anhydride were treated with sodium ethoxide to afford 6-substituted 1-(6-substituted 4-phenyl-2-quinolyl)-4-phenyl-2(1*H*)-quinolone derivatives (IX).

The yields, physical properties, and results of the elemental analyses of VIII and IX are listed in Table 2.

Whereas the NMR spectra of the acetyl quinolines, VIII, in deuteriochloroform reveal no peaks at δ 6.5—6.9 ppm, those of the 1-quinolyl-2(1*H*)-quinolones, IX, show the peaks at δ 6.72—6.77 ppm which are assigned to CH at the 3-position of the quinolone ring.

Experimental

All the melting points are uncorrected. The NMR spectra were determined on a Hitachi R-20 spectrometer.

Materials. The 2-aminobenzophenone (Ia) was prepared according to the method of Scheifele and DeTar;[6] mp 104—105°C (lit,[6] mp 105—106°C). The 2-amino-5-methylbenzophenone (Ib) was prepared by the method of Staskun;[7] mp 66—67°C (lit,[7] mp 66—67°C). The 2-amino-5-chlorobenzophenone (Ic) was prepared by the method of Sternbach *et al.*;[8] mp 100—101°C (lit,[7] mp 100—101°C).

The 2,6-dichloro-4-phenylquinoline (V) was prepared in the following way. 2-Acetamido-5-chlorobenzophenone (IIIc), which had been obtained by the acetylation of Ic, was treated with sodium ethoxide to give 6-chloro-4-phenyl-2(1*H*)-quinolone (IV). The treatment of IV with phosphorus oxychloride in the presence of dry pyridine at 130—140°C gave V; mp 111—112°C (lit,[9] mp 114—115°C).

The PPA was obtained from the Wako Pure Chemical Industries Co., Ltd.

The Reaction of 2-Aminobenzophenones (I) with Aliphatic Acids. Only a typical reaction will be described here. All of these reactions were carried out by a method similar to that described below.

A mixture of 2-amino-5-chlorobenzophenone(5 mmol), acetic acid (15 mmol), and PPA (20 g) was heated to 140—145°C for 15 min. After cooling, the reaction mixture was poured into ice water (*ca.* 100 m*l*), neutralized with 28% ammonia water, and extracted with methylene chloride (*ca.* 100 m*l*). The extract was then washed with water and dried over anhydrous magnesium sulfate. The solution was concentrated to 30 m*l* and chromatographed on silica gel with the same solvent. The first eluate (*ca.* 100 m*l*) was evaporated to dryness, and the resulting solid was recrystallized from a mixture of methylene chloride and methanol to afford IIc as yellow needles.

2-(2-Benzoyl-4-chloroanilino)-6-methyl-4-phenylquinoline (IIm). A mixture of Ib (4 mmol), IIIc (4 mmol), and PPA (20 g) was heated to 135—140°C for 30 min. The reaction mixture was worked up according to the procedure described for the preparation of IIc. Recrystallization from a mixture of methylene chloride and methanol afforded IIm as yellow needles.

2-(2-Benzoyl-4-methylanilino)-6-chloro-4-phenylquinoline (IIn). *i) From IIIb.* A mixture of Ic (4 mmol), IIIb (4 mmol), and PPA (20 g) was heated to 155—160°C for 1 hr. The reaction mixture was then worked up according to the procedure described for the preparation of IIc. Recrystallization from a mixture of methylene chloride and methanol afforded IIn as yellow needles.

ii) From V. A mixture of Ib (4 mmol), V (4 mmol), and copper powder (20 mg) was sealed into a glass ampoule and then heated at 175—180°C for 5 hr. After the ampoule had been cooled and opened, the reaction mixture was dissolved in methylene chloride (*ca.* 20 m*l*) and filtered to remove the catalyst. The

6) H. J. Scheifele, Jr., and D. F. DeTar, "Organic Syntheses," Coll. Vol. IV, p. 34 (1962).
7) B. Staskun, *J. Org. Chem.*, **29**, 2856 (1964).
8) L. H. Sternbach, E. Reeder, O. Keller and W. Metlesics, *ibid.*, **26**, 4488 (1961).
9) G. A. Reynolds and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 1852 (1950).

solution was then chromatographed on silica gel with the same solvent. The first eluate (*ca.* 100 m*l*) was evaporated to dryness, and the resulting solid was recrystallized from a mixture of methylene chloride and methanol to afford IIn as yellow needles.

The product was identified by means of mixed-melting-point measurements and by a comparison of its IR and NMR spectra with those of the sample obtained from *i*.

Acetylation of IIa, IIb, and IIc. A typical experiment will be described below.

A solution of IIc (2 mmol) in acetic anhydride (25 m*l*) was heated at 75—80°C in the presence of sodium acetate (2 g). After 1 hr, the mixture was cooled to room temperature and kept overnight. Then the solution was poured into ice water and extracted with chloroform. The extract was successively washed with water, a 5% sodium hydrogencarbonate solution, and water. The solution was dried over anhydrous magnesium sulfate and then evaporated to dryness. The residual oil was solidified by adding a small amount of methylene chloride, and the resulting solid was recrystallized from a mixture of methylene chloride and methanol to afford VIIIc as white prisms.

VIIIa and VIIIb were also obtained according to methods similar to that described above.

General Procedure for the Preparation of 1-Quinolyl-2(1*H*)-quinolone (IX). Into a solution of VIII (1.5 mmol) in absolute ethanol (120 m*l*), a sodium ethoxide solution [from sodium (0.1 g) and absolute ethanol (20 m*l*)] was stirred, drop by drop, at 75—80°C over a 15 min period. After having been stirred for an additional 15-min, the reaction mixture was poured into water. The crude product was collected by filtration and washed with warm water. Recrystallization from carbon tetrachloride afforded 6-substituted 1-(6-substituted 4-phenyl-2-quinolyl)-4-phenyl-2(1*H*)-quinolones (IX) as white prisms.

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