

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

## Effect of *N*-Alkyl on Formation of Quinolones from *N*-Alkylbenzoylacetanilides<sup>1</sup>

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*N*-Alkylbenzoylacetanilides cyclize to *N*-alkyl-4-phenyl-2-quinolones with sulfuric acid when the alkyl is primary, but not when it is secondary. Failure to cyclize probably results from steric inhibition of =N—Ar conjugation, an interpretation supported by ultraviolet properties of related *N*-alkyl-*p*-nitroacetanilides.

Experiments undertaken to develop a new synthesis of 4-phenylquinoline showed that *N*-methylacetanilide could be acylated with ethyl benzoate in presence of sodium ethoxide, but in low yield. The product, *N*-methylbenzoylacetanilide, reacted with concentrated sulfuric acid to form 1-methyl-4-phenyl-2-quinolone, which was converted into 4-phenylquinoline by standard methods.

When *N*-*iso*-propylacetanilide was treated with ethyl benzoate and sodium ethoxide, *N*-*iso*-propylbenzoylacetanilide was formed in good yield. Surprisingly, however, the latter compound was recovered unchanged when it was treated with sulfuric acid.

The object of the present work was to determine why the cyclization failed. It has been found that

the class of alkyl group in an *N*-alkylbenzoylacetanilide affects reactivity towards sulfuric acid. When the alkyl is primary (methyl, ethyl, *n*-propyl, *n*-butyl, and *iso*-butyl), the corresponding *N*-alkylquinolone is formed. When it is secondary (*iso*-propyl, *sec*-butyl), no cyclization takes place. When it is tertiary (butyl), it is lost, and unsubstituted 4-phenylquinolone is formed. These qualitative results were substantiated by kinetic studies (Table I).

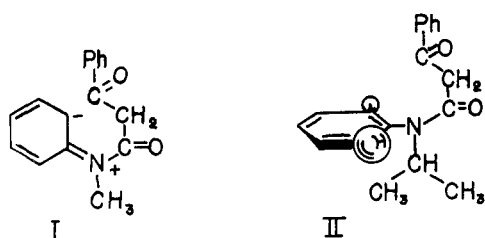
In order to account for the results, it may be assumed that the protonated carbonyl group attacks the benzene ring only when the nitrogen atom can furnish electrons to the *ortho* position (I). When a bulky *N*-alkyl is present, the ring is hindered from being coplanar with the nitrogen valences (II), a double bond cannot form, and cyclization does not occur.

(1) From the Ph.D. Thesis of J. W. Britain, August 1950.

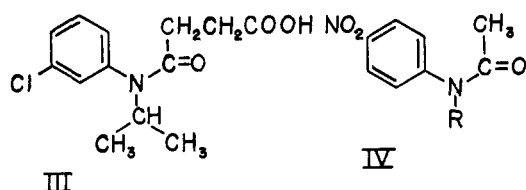
TABLE I  
KINETICS OF CYCLIZATION OF *N*-ALKYLBENZOYLACETANILIDES

Alkyl	Temp., °C.	Time, Min.	Prods. <sup>a</sup> g.	Completion %	Acetophenone %	10 <sup>4</sup> K <sup>b</sup> sec. <sup>-1</sup>
CH <sub>3</sub> <sup>c</sup>	60.1	33	4.53	40.1	<1	2.60
	75.3	19.5	4.54	58.8	<1	7.59
	76.2	30	4.36	75.5	<1	7.83
	77.5	32	4.68	81.1	<1	7.78
	88.2	30	4.30	99.3	<1	27.60
C <sub>2</sub> H <sub>5</sub> <sup>d</sup>	63.2	30	0.90 <sup>e</sup>	19.9	2.9	1.23
	74.9	15	4.35	23.7	10.3	3.01
	74.8	30	4.66	41.1	11.2	2.94
	88.7	30	4.35	80.5	<1	9.09
	63.3	30	0.89 <sup>e</sup>	15.3	4.3	0.92
<i>n</i> -C <sub>3</sub> H <sub>7</sub> <sup>f</sup>	75.2	15	3.81 <sup>g</sup>	18.7	12.9	2.30
	75.2	30	4.54	36.5	14.3	2.52
	88.9	30	4.42	78.4	<1	8.53
	74.8	16	0.95 <sup>e</sup>	<1	7.0	<0.10
	74.5	30	0.95 <sup>e</sup>	<1	4.6	<0.05
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	88.3	30	4.44	4.0	6.7	0.23
	63.5	30	0.87 <sup>e</sup>	16.6	<1	1.01
	75.1	16	0.90 <sup>e</sup>	19.2	<1	2.22
	74.8	30	0.84 <sup>e</sup>	32.6	9.9	2.19
	89.6	30	4.39	82.8	<1	9.79
<i>n</i> -C <sub>4</sub> H <sub>9</sub> <sup>h</sup>	62.4	30	0.93 <sup>e</sup>	10.0	26.5	0.59
	75.5	15	0.87 <sup>e</sup>	17.4	21.1	2.13
	74.5	30	0.85 <sup>e</sup>	29.2	22.2	1.93
	88.8	30	2.47 <sup>i</sup>	73.2	5.3	7.32
	74.8	15	4.35	<1	1.6	0.11
<i>s</i> -C <sub>4</sub> H <sub>9</sub>	74.7	30	4.77	0.6	3.3	0.03

<sup>a</sup> From 5 g. of anilide, unless otherwise noted. <sup>b</sup>  $k = [2.303/(t_2 - t_1)] \log C_1/C_2$ . <sup>c</sup>  $H^\ddagger = 19.3$  cal.,  $\Delta S^\ddagger = -19.7$  e.u. <sup>d</sup>  $H^\ddagger = 18.5$  cal.,  $\Delta S^\ddagger = -23.9$  e.u. <sup>e</sup> From 1 g. of anilide. <sup>f</sup>  $H^\ddagger = 20.1$  cal.,  $\Delta S^\ddagger = -19.6$  e.u. <sup>g</sup> From 4 g. of anilide. <sup>h</sup>  $H^\ddagger = 20.1$  cal.,  $\Delta S^\ddagger = -19.6$  e.u. <sup>i</sup>  $H^\ddagger = 22.5$  cal.,  $\Delta S^\ddagger = -13.0$  e.u. <sup>j</sup> From 3 g. of anilide.



If the barrier to phenyl rotation were high enough, it would be possible to resolve a properly substituted analog of II. But *m*-chloro-*N*-*iso*-propylsuccinylanilic acid (III) formed a homogeneous crystalline salt with cinchonidine, and the acid regenerated from this salt was optically inactive.



Support for the suggestion of a structure like II, however, was found in a comparison of the ultraviolet spectra of *N*-*iso*-propyl-*p*-nitroacetanilide (IV) and other nitro compounds (Table II). It is apparent that the bulky *iso*-propyl group completely inhibits amide-nitro conjugation, indicating hindrance to coplanarity. It is thus probable that a similar effect prevents ring closure in *N*-*sec*-alkylbenzoylacetanilides.

TABLE II  
SPECTRA OF *p*-SUBSTITUTED NITROBENZENES

Substituent	$\lambda_{\max}$	$\epsilon$	Reference
H—	268	$7.8 \cdot 10^3$	Doub and Vanderbelt, <i>J. Am. Chem. Soc.</i> , 69, 2714 (1947).
CH <sub>3</sub> —	285	$9 \cdot 10^3$	<i>Ibid.</i>
CH <sub>2</sub> NAc	288	$1.1 \cdot 10^4$	Present work.
C <sub>2</sub> H <sub>5</sub> NAc	285		Masaki, <i>Bull. Chem. Soc. Japan</i> , 7, 313 (1932).
(CH <sub>3</sub> ) <sub>2</sub> CHNAc	265	$7 \cdot 10^3$	Present work.

#### EXPERIMENTAL

*N*-Methylbenzoylacetanilide. (a). A suspension of sodium ethoxide from 2.3 g. of powdered sodium and 7 ml. of alcohol in 50 ml. of toluene was treated with 15 g. of ethyl benzoate and 15 g. of *N*-methylacetanilide. The mixture was heated for 90 min. under a 20-cm. Vigreux column at such a rate that the temperature at the top of the column was 78–83°, 14.5 ml. of distillate being collected. The mixture was then neutralized with acetic acid and steam distilled, removing toluene and 3.3 g. of methylaniline. The residue was taken up in ether and shaken with 40 ml. of 15% sodium hydroxide. The crystalline sodium salt was removed and decomposed with dilute hydrochloric acid giving 6.6 g. (26%) of colorless prisms m.p. 97–98° (from alcohol).

(b). A mixture of 96 g. of ethyl benzoylacetate, 53.5 g. of *N*-methylaniline and 100 ml. of xylene was heated for 2 hr. in a bath at 170° under a Vigreux column, about 20 ml. of distillate being collected. To complete the reaction, it was found necessary to heat for an additional 20 hr. at 140°, and then for some time at 190–200° while the remaining volatile material was allowed to distill. Crystallization from ligroin gave 85 g. (67%) of crude product, m.p. 94–97°, and recrystallization from alcohol gave the pure anilide, m.p. 97–98°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>: C, 75.9; H, 5.93. Found: C, 76.0; H, 6.14.

The ultraviolet spectrum in alcohol had absorption peaks at 240 and 300  $m\mu$  ( $\epsilon = 12,200$  and 6,700). With alcoholic ferric chloride, the anilide gave a red-purple color. When 0.5 g. of it was dissolved in 5 ml. of cold acetic acid and treated with 0.2 g. of sodium nitrite in a little water, it was converted into  $\alpha$ -oximino-*N*-methylbenzoylacetanilide, fine white needles from alcohol, m.p. 183–185°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 68.1; H, 5.00. Found: C, 67.8; H, 4.97.

*N*-Ethylbenzoylacetanilide was obtained in 56% yield from 96 g. of ethyl benzoylacetate and 60 g. of *N*-ethylaniline in hot xylene; m.p. 73–75°;  $\lambda_{\max}^{\text{EtOH}}$ , 243 (11,900), 297 (7,200).

*Anal.* Calcd. for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>: C, 76.4; H, 6.41; N, 5.24. Found: C, 76.8, 76.6; H, 6.76, 6.57; N, 5.26.

*N*-*n*-Propylbenzoylacetanilide was obtained in 30% yield from 64 g. of ethyl benzoylacetate and 45 g. of *N*-*n*-propylaniline; m.p. 94–95°;  $\lambda_{\max}^{\text{EtOH}}$ , 243 (11,500), 300 (7,000).

*Anal.* Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>: C, 76.8; H, 6.81. Found: C, 76.9; H, 7.13.

*N*-*iso*-Propylbenzoylacetanilide, from sodium ethoxide, ethyl benzoate, and *N*-*iso*-propylacetanilide in toluene in 75% yield or from ethyl benzoylacetate and *iso*-propylaniline in hot xylene in fair yield, formed coarse needles from alcohol, m.p. 91–92°;  $\lambda_{\max}^{\text{EtOH}}$ , 245 (11,000), 295 (6,300).

*Anal.* Calcd. for C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>: C, 76.8; H, 6.81; N, 4.98. Found: C, 77.0, 77.2; H, 7.03, 6.81; N, 4.95.

The copper salt formed yellow-green prisms from toluene m.p. 235–237°.

*Anal.* Calcd. for C<sub>26</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>Cu: Cu, 10.2. Found: Cu, 10.2.

The  $\alpha$ -oximino derivative formed faintly yellow needles from alcohol that sintered at 200° and decomposed at 208–211°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: C, 69.7; H, 5.85. Found: C, 69.6; H, 5.81.

*N*-*n*-Butylbenzoylacetanilide, colorless prisms from ligroin and then alcohol, was obtained in 15% yield from 96 g. of ethylbenzoylacetate and 75 g. of *n*-butylaniline in hot xylene; m.p. 71–73°;  $\lambda_{\max}^{\text{EtOH}}$ , 245 (12,000), 300 (7,000).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub>: C, 77.2; H, 7.17; N, 4.75. Found: C, 77.5; H, 7.43; N, 5.10.

*N*-*iso*-Butylbenzoylacetanilide was obtained in 47% yield from 37 g. of ethylbenzoylacetate and 28 g. of *iso*-butylaniline<sup>2</sup> in hot xylene; colorless prisms from ether, m.p. 96–98°;  $\lambda_{\max}^{\text{EtOH}}$ , 240 (12,000), 300 (8,500).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub>: C, 77.2; H, 7.17. Found: C, 77.5; H, 7.32.

*N*-*sec*-Butylbenzoylacetanilide was obtained in 73% yield from 200 g. of ethyl benzoylacetate and 160 g. of *sec*-butylaniline in hot xylene; colorless crystals from ether, m.p. 68–70°;  $\lambda_{\max}^{\text{EtOH}}$ , 242 (11,300), 297 (7,500).

*Anal.* Calcd. for C<sub>19</sub>H<sub>21</sub>NO<sub>2</sub>: C, 77.2; H, 7.17. Found: C, 77.5; H, 7.34.

*N*-*tert*-Butylbenzoylacetanilide was obtained in 19% yield from 7.5 g. of ethylbenzoylacetate and 5.7 g. of *tert*-butyl-

(2) *iso*-Butylaniline was purified through its hydrochloride, colorless plates from alcohol, m.p. 205–207°; C<sub>10</sub>H<sub>14</sub>ClN requires C, 64.7; H, 8.69; found: C, 64.7, 64.8; H, 8.86, 8.53.

aniline<sup>3</sup> in hot xylene; colorless prisms from ether, m.p. 94–96°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 235 (10,000), 300 (7,800).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{21}\text{NO}_2$ : C, 77.2; H, 7.17. Found: C, 77.3; H, 7.33.

When 0.2 g. of this anilide was heated at 75° for 30 min. with 1 ml. of concentrated sulfuric acid, there was obtained 0.13 g. of 4-phenyl-2-quinolone.

*1-Methyl-4-phenyl-2-quinolone*. A mixture of 7 g. of *N*-methylbenzoylacetanilide and 20 ml. of concentrated sulfuric acid was heated at 100° for 1 hr. and then poured on ice. The precipitate was washed with dilute sodium carbonate, dried (6.2 g., m.p. 93–120°), and crystallized from dilute alcohol, giving colorless needles (3.6 g., 55%), m.p. 141–142°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 230 (37,500), 280 (5,900), 340 (5,500). The quinoline gave no color with ferric chloride.

Anal. Calcd. for  $\text{C}_{16}\text{H}_{18}\text{NO}$ : C, 81.0; H, 5.56. Found: C, 81.0; H, 5.76.

*1-Ethyl-4-phenyl-2-quinolone*, yield 71%, had m.p. 98–99°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 230 (40,000), 280 (7,500), 335 (6,200).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{18}\text{NO}$ : C, 81.9; H, 6.07. Found: C, 82.0, 81.5; H, 6.40, 6.19.

*1-n-Propyl-4-phenyl-2-quinolone*, crude yield 94%, had to be freed of impurity that gave a purple ferric chloride test by chromatography over alumina using ether and ligroin. The pure substance, yield 83%, had m.p. 73–74°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 230 (39,000), 280 (7,500), 335 (6,500).

Anal. Calcd. for  $\text{C}_{18}\text{H}_{20}\text{NO}$ : C, 82.1; H, 6.51. Found: C, 82.0; H, 6.67.

*1-n-Butyl-4-phenyl-2-quinolone*, crude yield 87%, yield after chromatography 40%, had m.p. 71–72°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 230 (40,000), 280 (6,000), 335 (5,500).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{NO}$ : C, 82.3; H, 6.90. Found: C, 82.3; H, 7.15.

*l-iso-Butyl-4-phenyl-2-quinolone*, crude yield 68%, yield after recrystallization from ether 35%, had m.p. 83–84°;  $\lambda_{\text{max}}^{\text{EtOH}}$ , 235 (42,500), 280 (7,500), 335 (6,000).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{NO}$ : C, 82.3; H, 6.90. Found: C, 82.6; H, 7.07.

After treatment with sulfuric acid at 100°, the remaining anilides were unchanged: *iso*-propyl-, recovery 96%, *sec*-butyl-, recovery 85%.

*Kinetic experiments* (see Table I). A quantity (usually 5 g.) of *N*-alkylbenzoylacetanilide was stirred rapidly into four parts (ml./g.) of 96% sulfuric acid which had been brought to temperature. After the desired time, the reaction was stopped by stirring the mixture into ice, and the precipitate was taken up in ether. The ether solution was washed with bicarbonate and evaporated, and a portion of the weighed residue was diluted to a definite volume with alcohol. Analyses of the products were made using a Beckmann spectrophotometer, by comparing the observed ultra

(3) *tert*-Butylaniline was prepared by Hickenbottom's method [*J. Chem. Soc.*, 946 (1933)] and purified by fractional crystallization of its *picrate*, yellow crystals from benzene and then alcohol, m.p. 184–185° ( $\text{C}_8\text{H}_{13}\text{N}_4\text{O}_7$  requires: C, 50.8; H, 4.76; N, 14.8; found: C, 51.0; H, 4.98; N, 14.98); yield, 5.75 g. of pure amine from 500 g. of *tert*-butyl iodide.

violet spectra with those of the pure components. The method used was similar to the one recently described by Dewar and Urch,<sup>4</sup> in which complete curves, rather than isolated points, were combined to reproduce the observed one. The odor of acetophenone was apparent in some of the reaction mixtures, and this compound was identified by isolation,  $\lambda_{\text{max}}^{\text{EtOH}}$ , 240 (13,000), 280 (1,000), and as its dinitrophenylhydrazone. Since quantitative studies indicated that acetophenone was formed in erratic fashion, it is probable that it was formed after the reaction mixtures were quenched. Since the quinolones containing *N*-*iso*-propyl- and *N*-*sec*-butyl groups were not formed in insoluble amount, it was assumed that their spectra would be an average of the nearly identical spectra of the 1-*n*-alkylquinolones.

*m*-Chloro-*N*-*iso*-propylaniline. A mixture of 95 g. of *iso*-propyl bromide and 200 g. of *m*-chloroaniline was heated under reflux until the temperature of the mixture had reached 150°. The mixture was then cooled and shaken with 300 ml. of 15% sodium hydroxide and the amine was separated and shaken with a solution of 150 g. of zinc chloride in 150 ml. of water. Excess zinc chloride solution was then decanted, and the remaining cheesy mass was extracted with 4 × 200 ml. of 30–60° ligroin. Distillation gave 111 g. of colorless product, b.p. 109–111° at 11 mm.

Anal. Calcd. for  $\text{C}_9\text{H}_{10}\text{ClN}$ : C, 63.6; H, 7.00. Found: C, 63.7; H, 7.08.

*m*-Chloro-*N*-*iso*-propylsuccinanic acid. A mixture of 16 g. of amine with 9.7 g. of succinic anhydride heated for 3 hr. at 105° gave 23.4 g. of product, colorless needles from dilute acetic acid, m.p. 132–134°.

Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}\text{ClNO}_3$ : C, 58.0; H, 5.95. Found: C, 58.4; H, 5.99.

The *cinchonidine salt* separated in cotton-like needles in a yield of 50% when a solution of 2.5 g. of the acid and 2.5 g. of cinchonidine in 25 ml. of hot ethyl acetate was treated with 30 ml. of 30–60° ligroin and kept at room temperature for a week. It had  $[\alpha]_D^{25} -60^\circ$  ( $\text{CHCl}_3$ ,  $C = 3$ ).

Anal. Calcd. for  $\text{C}_{13}\text{H}_{16}\text{ClNO}_3 + \text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ : C, 68.2; H, 6.81. Found: C, 68.0; H, 7.02.

The acid was regenerated at below 10° and examined within 3.5 min., but neither the crystalline cinchonidine salt nor the material remaining in the mother liquor furnished an active product.

*N*-*iso*-Propyl-*p*-nitroacetanilide. A solution of 25 g. of *N*-*iso*-propylacetanilide in 50 ml. of concentrated sulfuric acid was stirred at 15° and treated dropwise with 10 ml. of nitric acid (1.42) in 10 ml. of sulfuric acid. After 10 min., the mixture was poured on ice; the resulting oil crystallized when it was rubbed with a little ether. Fractional crystallization from ethyl acetate gave 12.2 g. of a mixture, m.p. 60–69°, which was discarded, and 7.9 g. of pure product, nearly colorless needles, m.p. 103–104°.

Anal. Calcd. for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$ : C, 59.5; H, 6.35. Found: C, 59.9; H, 6.38.

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(4) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957).