

DECOMPOSITION OF SOME 2-ARYL-4-QUINOLYL  
DIAZOMETHYL KETONES AS A ROUTE TO  
2-ARYL-4-QUINOLYL ACETIC ACID DERIVATIVES

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2-aryl-quinoline-4-carboxylic acids as the components to begin with, have been prepared by the use of two methods: Pfitzinger (1) and Knoevenagel (2) and their melting points have been compared with values obtained from the literature. The chlorides of these acids may be converted to corresponding diazomethyl ketones by interaction with diazomethane. The silver-oxide catalyzed decomposition (Wolff's rearrangement) (3) of several 2-aryl-4-quinolyl diazomethyl ketones in slightly basic media yielded 2-aryl-4-quinolyl-acetic acid derivatives.

Although there exist numerous methods for converting an acid to its next higher homolog or to a derivative of the homologous acid, such as an ester or amide, it is apparent that by the Arndt-Eistert synthesis (4) can be carried through rapidly, one day usually being sufficient for the complete synthesis, and it is thus an ideal method when only small amounts of the final product are desired.

The synthesis, which is applicable to both aliphatic and aromatic acids, involves the following three operations:

1. Formation of acid chlorides
2. Reaction of acid chlorides with diazomethane to yield a diazoketone.
3. Rearrangement of diazoketone with loss of nitrogen, in the presence of suitable reagents and a catalyst.

The discovery that diazoketones can be converted into derivatives of an acid was made by Wolff and this phase of the synthesis is known as the Wolff's rearrangement.

The use of diazoketones as intermediate reagents for converting an acid to its next higher homolog has been studied intermitently since 1912, when Wolff found, for example, that the treatment of  $\alpha$ -diazoacetophenone,  $C_6H_5-CO-CHN_2$ , with ethanolic ammonia and silver oxide gave phenylacetamide,  $C_6H_5-CH_2-CONH_2$ , in good yield.

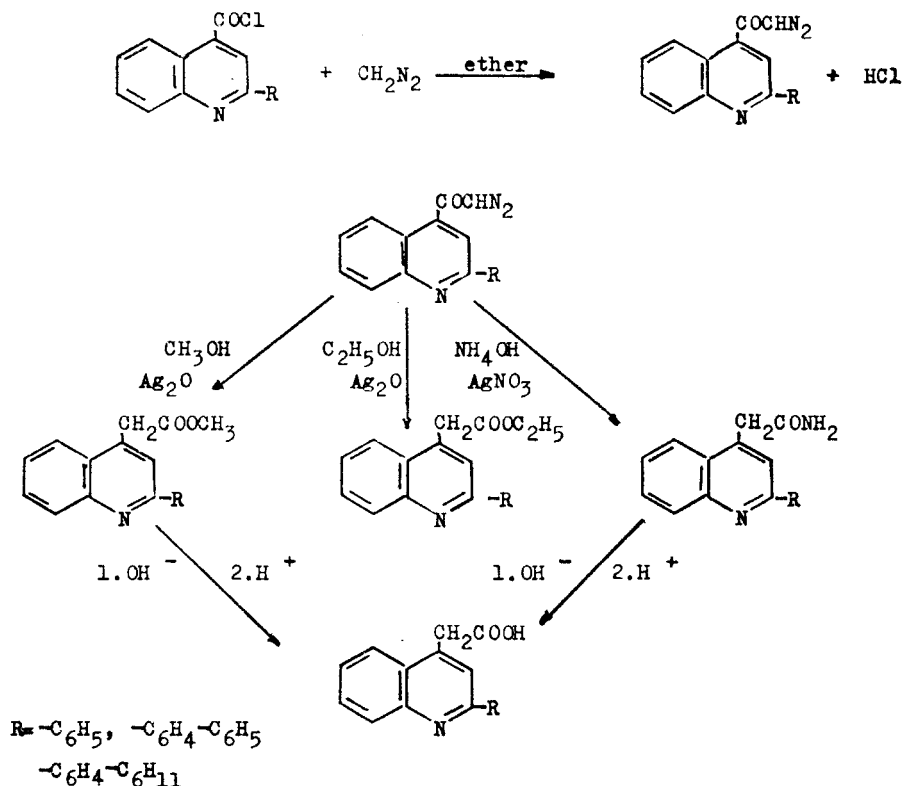
It occurred to us that 2-aryl-quinolyl-4-diazomethyl ketones would possess sufficient reactivity to serve as reagents in order to provide a synthetic route to 2-aryl-4-quinolyl-acetic acids and their derivatives such as esters or amides.

This paper reports the results of these studies.

## RESULTS

2-aryl-quinolyl-4-carboxylic acids used in these studies are conveniently prepared by Pfitzinger reaction (1) from isatin and the corresponding methyl-aryl ketone; acid chlorides were prepared from acid and thionyl chloride. The esterification of acid chlorides with alcohol, or of acids with ethereal solution of diazomethane was the procedure for the preparation of numerous esters. The acid chlorides were converted to 2-aryl-quinolyl-4-diazomethyl ketones (aryl = phenyl, 4'-cyclohexylphenyl, 4'-biphenyl) by treating them with ethereal solution of diazomethane. A list of these preparations is given in Table I.

The silver-oxide catalized decomposition of these diazomethyl ketones gives the corresponding 2-aryl-quinolyl-4-acetic acid derivatives. For example, when 2-(4'-cyclohexylphenyl)-quinolyl-4-diazomethyl ketone was refluxed with anhydrous methanol in the presence of silver oxide for a few hours and the reaction mixture crystallized, a light yellow solid remained, which melted at 170—171°C after recrystallization from methanol (comp. *j*, Table II). Prolonged hydrolysis with concentrated potassium hydroxid converted this compound to a corresponding 2-(4'-cyclohexylphenyl)-quinolyl-4-acetic acid (comp. *i*, Table II). The conversion to an acid amide, 2-(4'-cyclohexylphenyl)-quinolyl-4-acetamide, is contained in treating a warm solution of corresponding diazomethyl ketone in dioxane with 28% aqueous solution of ammonia containing a small amount of silver nitrate, after which the mixture is heated for some time; potassium hydroxide hydrolysis resulted in the formation of 2-(4'-cyclohexylphenyl)-quinolyl-4-acetic acid.



The other 2-aryl-quinolyl-4-diazomethyl ketones were degraded in a manner similar to that depicted in Chart I, in order to establish their identities. The corresponding methyl or ethyl-2-aryl-quinolyl-4-acetates, 2-aryl-quinolyl-4-acetamides or 2-aryl-quinolyl-4-acetic acids were not previously reported.

These results suggested that the decomposition of 2-aryl-quinolyl-4-diazomethyl ketones in methanol, ethanol or concentrated ammonia in the presence of silver oxide or silver nitrate might render a convenient method for the preparation of 2-aryl-quinolyl-4-acetic acid derivatives, compounds which have been of great interest in our investigations as substances with potential physiological activity.

An attempt to extend this decomposition to 2-phenyl-quinolyl-4-diazomethyl ketone hydrochloride (m. p. 170—71°) did not give the results which were expected. It is of interest to note that this diazomethyl ketone hydrochloride formed exclusively 2-phenyl-quinolyl-4-carboxamide, not 2-phenyl-quinolyl-4-acetamide, which resulted from the decomposition in dioxane with 28% aqueous solution of ammonia and a small

amount of silver nitrate. The amide was also hydrolysed to the corresponding acid, 2-phenyl-quinolyl-4-carboxylic acid (atophane) for identification.

The IR-spectra of 2-aryl-quinolyl-4-carboxylic acids, 2-aryl-quinolyl-4-acetic acids and their esters showed C=O stretching vibration frequency at 1700—1740  $\text{cm}^{-1}$ ; absorption, due to C—O stretching, is observed in the 1250  $\text{cm}^{-1}$  and bonded O—H stretching absorption in the region 2500—2800  $\text{cm}^{-1}$ . All amides show a carbonyl absorption (amide I band) in the region 1680—1700  $\text{cm}^{-1}$  and two medium-intensity NH-stretching frequencies corresponding to the asymmetrical and symmetrical vibration of the hydrogen atoms in the  $\text{NH}_2$ -group occur near 3100—3350  $\text{cm}^{-1}$ .

## EXPERIMENTAL

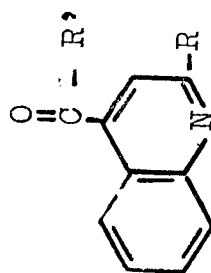
Preparation of 2-aryl-quinolyl-4-carboxylic acids.—A mixture of 0,1 mole of the methyl-aryl ketone (p-phenylacetophenone, p-cyclohexylacetophenone), 0,1 mole of the isatin and 0,3 mole of the potassium hydroxide in the 10 ml of water and 50 ml ethanol was refluxed for 24 hrs, after which the excess of ethanol was removed by distillation and a dark-red residue was cooled, diluted with water (200 ml), and acidified with glacial acetic acid. The crude product was filtered from the mixture, washed with water and dried. Recrystallization from glacial acetic acid or dioxane yielded pure 2-aryl-quinolyl-4-carboxylic acids.

The acids showed the characteristic infrared C=O absorption in the form of an intensity band in the range 1710—1725  $\text{cm}^{-1}$ , C—O stretching at or near 1250  $\text{cm}^{-1}$  and bonded O—H stretching absorption in the region 2500—2700  $\text{cm}^{-1}$ .

Preparation of 2-aryl-quinolyl-4-diazomethyl ketones.—0,01 mole of the 2-aryl-4-quinolynoyl chloride was added slowly, stirring it for over 1 hr, during which time the flask was cooled in icy water, to an ethereal solution of diazomethane obtained from 4g of nitrosomethylurea. After 1—2 hrs at 0—5° and several hours at room temperature the crystalline yellow crude diazoketone was collected. Evaporation of ethereal filtrate yielded only 3—4% additional product. The melting was in all cases accompanied by decomposition.

Preparation of methyl and ethyl-2-aryl-quinolyl-4-acetates.—A small amount (0,15—0,2 g) of a slurry of silver oxide stirred with 5—10 ml anhydrous alcohol for 1 hr was added to a mixture of 0,005 mole corresponding diazoketone in 25—30 ml anhydrous alcohol (methanol or ethanol) at 60—65°. The mixture was then refluxed for 2—2½ hrs, during which time all of the rather insoluble diazoketone went into the solution. When the decomposition was complete, a small amount of Norit was added, the mixture was refluxed continually for another

Table I

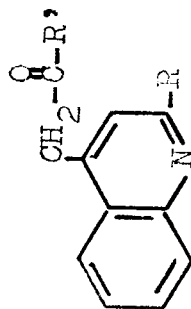


R

—C <sub>6</sub> H <sub>5</sub>	R'	—OH <sup>a</sup> 73	—OCH <sub>3</sub> <sup>b</sup> 97	—OC <sub>2</sub> H <sub>5</sub> <sup>c</sup> 90	—NH <sub>2</sub> <sup>d</sup> 94
	Yield %	210—212	61—62	51—52	196—197
	m. p. °C				
—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>5</sub>	R'	—OH <sup>e</sup> 98	—OCH <sub>3</sub> <sup>f</sup> 98	—OC <sub>2</sub> H <sub>5</sub> <sup>g</sup> 85	—NH <sub>2</sub> <sup>j</sup> 92
	Yield %	293—294	146—147	134—135	251—252
	m. p. °C				
—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>11</sub>	R'	—OH <sup>k</sup> 98	—OCH <sub>3</sub> <sup>l</sup> 98	—OC <sub>2</sub> H <sub>5</sub> <sup>m</sup> 98	—NH <sub>2</sub> <sup>p</sup> 92
	Yield %	282—283	160—161	104—105	181—182
	m. p. °C				

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Table II



R

—C <sub>6</sub> H <sub>5</sub>	R' Yield % m. p. °C	—OH <sup>a</sup> 90 220—221	—OCH <sub>3</sub> <sup>b</sup> 98 84—85	—OC <sub>2</sub> H <sub>5</sub> <sup>c</sup> 90 60—61	—NH <sub>2</sub> <sup>d</sup> 90 207—208
—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>5</sub>	R' Yield % m. p. °C	—OH <sup>e</sup> 98 223—224	—OCH <sub>3</sub> <sup>f</sup> 70 164—165	—OC <sub>2</sub> H <sub>5</sub> <sup>g</sup> 82 118—119	—NH <sub>2</sub> <sup>h</sup> 90 229—230
—C <sub>6</sub> H <sub>4</sub> —C <sub>6</sub> H <sub>11</sub>	R' Yield % m. p. °C	—OH <sup>i</sup> 97 230—231	—OCH <sub>3</sub> <sup>j</sup> 72 170—171	—OC <sub>2</sub> H <sub>5</sub> <sup>k</sup> 86 137—138	—NH <sub>2</sub> <sup>l</sup> 90 262—263

<sup>a</sup> Anal. Calcd. for: C<sub>17</sub>H<sub>13</sub>NO<sub>2</sub>: C 77,55 H 4,98 N 5,32. Found: C 77,32 H 4,75 N 5,41. <sup>b</sup> Anal. Calcd. for C<sub>18</sub>H<sub>15</sub>NO<sub>2</sub>: C 77,96 H 5,45 N 5,05. Found: C 77,72 H 5,40 N 5,23. <sup>c</sup> Anal. Calcd. for C<sub>19</sub>H<sub>17</sub>NO<sub>2</sub>: C 78,33 H 5,88 N 4,81. Found: C 78,09 H 5,58 N 4,63. <sup>d</sup> Anal. Calcd. for C<sub>17</sub>H<sub>13</sub>N<sub>2</sub>O: C 77,84 H 5,38 N 10,68. Found: C 78,09 H 5,63 N 10,14. <sup>e</sup> Anal. Calcd. for C<sub>23</sub>H<sub>17</sub>NO<sub>2</sub>: C 81,39 H 5,05 N 4,13. Found: C 81,15 H 5,35 N 4,23. <sup>f</sup> Anal. Calcd. for C<sub>24</sub>H<sub>19</sub>NO<sub>2</sub>: C 81,56 H 5,42 N 3,96. Found: C 81,34 H 5,30 N 3,71. <sup>g</sup> Anal. Calcd. for C<sub>25</sub>H<sub>21</sub>NO<sub>2</sub>: C 81,72 H 5,76 N 3,81. Found: C 81,98 H 6,04 N 3,98. <sup>h</sup> Anal. Calcd. for C<sub>29</sub>H<sub>19</sub>N<sub>2</sub>O: C 81,63 H 5,36 N 8,28. Found: C 81,76 H 5,50 N 8,47. <sup>i</sup> Anal. Calcd. for C<sub>23</sub>H<sub>23</sub>NO<sub>2</sub>: C 79,97 H 6,71 N 4,06. Found: C 80,01 H 6,85 N 4,34. <sup>j</sup> Anal. Calcd. for C<sub>24</sub>H<sub>25</sub>NO<sub>2</sub>: C 80,19 H 7,01 N 3,90. Found: C 80,27. H 7,35 N 3,94. <sup>k</sup> Anal. Calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>2</sub>: C 80,39 H 7,29 N 3,75. Found: C 80,24 H 7,33 N 3,79. <sup>l</sup> Anal. Calcd. for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O: C 80,20 H 7,02 N 8,13. Found: C 80,43 H 7,28 N 8,27.

5 min., filtered and cooled. On cooling, the product crystallized; then it was collected by suction filtration. The solid thus obtained was dried and recrystallized from methanol or ethanol after a treatment with a little Norit.

The IR-spectra of methyl- and ethyl-2-aryl-quinolyl-4-acetates showed the characteristic C=O absorption in the form of an intensity band in the range 1740—1750  $\text{cm}^{-1}$  and absorption, due to C—O stretching at 1200  $\text{cm}^{-1}$ .

Preparation of 2-aryl-quinolyl-4-acetamides. — A solution of 0,005 mole 2-aryl-quinolyl-4-diazomethyl ketone in 40 ml dioxane was treated with 20 ml 28% aqueous solution of ammonia and 6—7 ml 10% aqueous silver nitrate solution at 60—70°. The mixture was boiled under reflux for 2—3 hrs. After that the mixture was filtered and cooled. The crude acetamide was precipitated by the addition of water. Recrystallization of the crude product from methanol gave pure 2-aryl-quinolyl-4-acetamides in good yield (90%).

The IR-spectra of 2-aryl-quinolyl-4-acetamides showed a strong C=O absorption band (amide I band) in the region of 1680—1700  $\text{cm}^{-1}$  and two medium-intensity NH-stretching frequencies occur near 3100  $\text{cm}^{-1}$  and 3350  $\text{cm}^{-1}$ . In all higher amides the weak band resulting from methylene vibration appeared in the region of 1460  $\text{cm}^{-1}$ .

Conversion of 2-aryl-quinolyl-4-acetamides to corresponding acids. — In a 100 ml round-bottom, one necked copper flask was placed 0,005 mole of a 2-phenyl-quinolyl-4-acetamide and 50 ml of 10% alcoholic potassium hydroxide (for 2-(4'-cyclohexylphenyl-) 400 ml, and 2-(4'-biphenyl-) 150 ml 10% alcoholic KOH). The mixture was refluxed until no evolution of ammonia was observed (6—7 hrs), which was followed by the distillation of the excess of ethanol, addition of water and acidification of the mixture. In this manner the 2-aryl-quinolyl-4-acetic acids listed in Table II were obtained.

In a similar manner, methyl-2-aryl-quinolyl-4-acetates were converted to corresponding acids.

The IR-spectra of 2-aryl-quinolyl-4-acetic acids showed C=O stretching vibration frequency at 1680—1740  $\text{cm}^{-1}$ ; C—O stretching in the region of 1250  $\text{cm}^{-1}$  and O—H stretching absorption in the region 2600—2800  $\text{cm}^{-1}$ .

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### РЕЗИМЕ

#### ДЕКОМПОЗИЦИЈА НА НЕКОИ 2-АРИЛ-4-ХИНОЛИЛ ДИАЗОМЕТИЛ КЕТОНИ КАКО ПАТ ДО ДЕРИВАТИ НА 2-АРИЛ-4-ХИНОЛИЛ ОЦЕТНИ КИСЕЛИНИ

М. ЛАЗАРЕВИЌ И М. ЈАНЧЕВСКА

2-арил-хинолил-4-карбонските киселини како појдошни компоненти во оваа работа беа добиени со употреба на две методи: Pfitzinger (1) и Knoevenagel (2), а нивните точки на топење беа споредени со вредностите најдени во литературата. Хлоридите на овие киселини можеа да бидат прведени во соодветни диазометил кетони при нивна реакција со етерски раствор на диазометан. Сребрениот оксид каталитичкото декомпонирање (Wolfi-ово пресметување) (3) на неколку 2-арил-4-хинолил диазометил кетони во алкална средина резултира во формирање на 2-арил-хинолил-4-оцетни киселини и некои нивни деривати како метил, етил естри и амиди.

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