

CCA-439

547.72:547.55:547.462.3

Original Scientific Paper

The Reaction of Arylfurfurylamines with Maleic Anhydride

D. Bilović

Department of Organic Chemistry, Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

Received June 10, 1966

The reaction of (2-furfuryl)-aniline (I) and (2-furfuryl)-*p*-toluidine (II) with maleic anhydride was investigated. The products were shown to be 2-phenyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic acid (V) and 2-*p*-tolyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic acid (VI). The suggestion is made that the reaction proceeds *via* formation of *N,N*-arylfurfuryl-maleamic acids (III and IV) followed by intramolecular Diels-Alder reaction.

In a previous paper¹ from this Laboratory it was reported that some allyl-aryl-(2-furfuryl)-amines, on standing at room temperature spontaneously isomerized to *N*-aryl-4H-5,7a-epoxyisoindolines, evidently formed by intramolecular Diels-Alder reaction. The present study continues our exploration of this type of reaction.

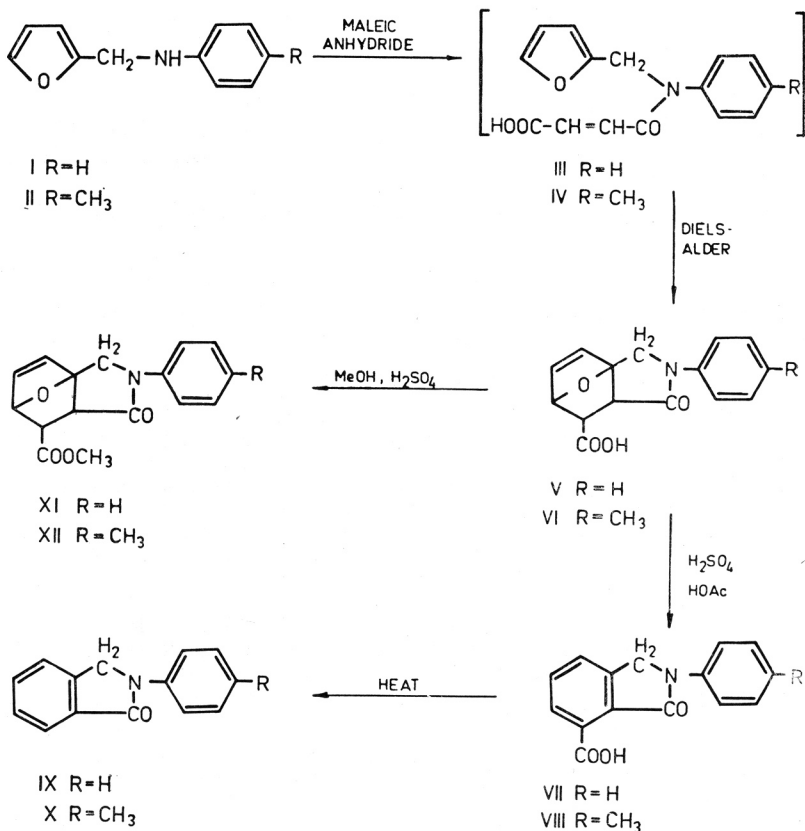
It is well known that primary and secondary amines react very readily with maleic anhydride giving the corresponding maleamic acid derivatives².

In our experiments, when (2-furfuryl)-aniline (I)³ and an excess of maleic anhydride was kept in ethanol overnight, a white crystalline compound, C₁₅H₁₃NO₄, m. p. 184—185° in a 96% yield was obtained. By titration with standard base the compound was proved to be a mono carboxylic acid.

This product was shown to be 2-phenyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic acid (V) identified by the following sequence of reactions: V was treated with sulfuric acid in glacial acetic acid yielding 2-phenyl-3-oxo-4-isoindolinecarboxylic acid (VII). Decarboxylation of VII on heating in boiling quinoline in the presence of copper powder gave *N*-phenylphthalimidine (IX), which proved to be identical with an authentic sample prepared according to Thiele and Schneider⁴.

The reaction of (2-furfuryl)-*p*-toluidine (II)³ with maleic anhydride under the same conditions showed the same behaviour as described for the *N*-phenyl analogue (I). 2-*p*-Tolyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic acid (VI) was obtained in a very good yield. On heating in a mixture of sulfuric and glacial acetic acid it was easily converted to 2-*p*-tolyl-3-oxo-4-isoindolinecarboxylic acid (VIII). Decarboxylation of VIII afforded *N*-*p*-tolylphthalimidine (X), which proved to be identical with an authentic specimen⁵.

The compounds V and VI were easily esterified with absolute methanol in the presence of sulfuric acid giving the corresponding methyl esters XI

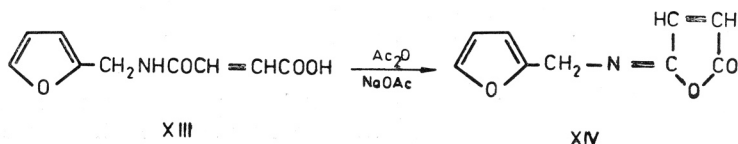


and XII. The products were converted by saponification to the starting acids V and VI.

The reaction of (2-furfuryl)-aniline and (2-furfuryl)-*p*-toluidine with maleic anhydride appears to take place through maleamic acids intermediates (III and IV) which readily convert to the compounds V and VI by an intramolecular Diels-Alder reaction.

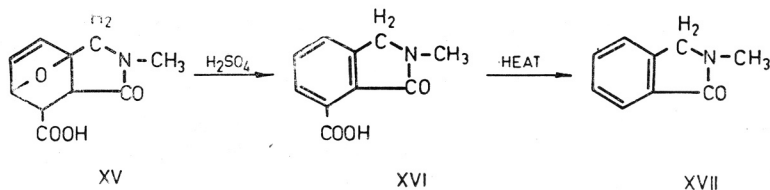
It was reported⁶ that furfurylamine and furfurylmethylamine react with maleic anhydride to yield *N*-furfurylmaleamic acid and *N,N*-furfurylmethylmaleamic acid respectively. However, in connection with our experiments we undertook a re-examination of this reaction and found that only in the first case the corresponding maleamic acid was formed.

The product (XIII) formed from furfurylamine and maleic anhydride exhibited a sharp IR band at 1020 cm.⁻¹ characteristic of the furan ring⁷. With acetic anhydride and anhydrous sodium acetate it was transformed into *N*-(2-furfuryl)-isomaleimide (XIV).



The structure of XIV was confirmed by the presence of two IR bands at 1795 cm^{-1} (the five membered ring lactone) and 1690 cm^{-1} (the carbon-nitrogen double bond).

The product formed from furfurylmethylamine and maleic anhydride showed an infrared spectrum similar to the spectra of compounds V and VI, while it was different from the spectrum of XIII. When it was treated with dilute sulfuric acid, the compound XVI, m. p. $203\text{--}204^{\circ}$, was obtained; XVI was decarboxylated to a crystalline product identified as *N*-methylphthalimidine XVII⁸.



Thus, the above experiments doubtlessly established that only with furfurylamine maleamic acid was obtained, while with the furfurylmethylamine the subsequent internal cyclization of the Diels-Alder type to the corresponding isoindolinecarboxylic acid XV took place.

EXPERIMENTAL

Melting points were determined on a Kofler heating microscope.

Materials

Maleic anhydride, m. p. 53° , a *Fluka purum* product, was used without further purification. The quinoline employed was *Fluka pract.* product and was purified by distillation *in vacuo*. A sample of furfurylmethylamine was kindly furnished by *Miles Chemical Company*, Elkhart, Indiana. Arylfurfurylamines were synthesized³.

2-Phenyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic Acid (V)

To a solution of (2-furfuryl)-aniline³ (4.0 g., 23.1 mmole) in 2.0 ml. of ethanol a solution of maleic anhydride (2.6 g., 26.6 mmole) in 12.0 ml. of ethanol was added dropwise, with occasional stirring. The solution which had turned from deep red to a yellow-orange colour was allowed to stand at room temperature overnight. The crystalline precipitate of V was filtered off and washed with ethanol. Yield 6.0 g. (96%), m. p. $181\text{--}182^{\circ}$. Two recrystallizations from ethanol gave colourless plates melting at $184\text{--}185^{\circ}$.

Anal. $\text{C}_{15}\text{H}_{13}\text{NO}_4$ (271.28) calc'd.: C 66.42, H 4.83, N 5.16%
 found: C 66.50, H 4.89, N 4.91%

Neutralization equivalent by titration with standard base calc'd.: 271.2; found: 269.3.

2-p-Tolyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic Acid (VI)

It was obtained as described for V. From (2-furfuryl)-*p*-toluidine³ (4.0 g., 21.4 mmole) and maleic anhydride (2.41 g., 24.6 mmole) the yield of VI was 5.4 g. (89%), m. p. $181\text{--}182^{\circ}$. Analytical sample, after two recrystallizations from ethanol, melted at $183\text{--}184^{\circ}$.

Anal. $\text{C}_{16}\text{H}_{15}\text{NO}_4$ (285.30) calc'd.: C 67.36, H 5.30, N 4.91%
 found: C 67.67, H 5.24, N 5.29%

Neutralization equivalent by titration with standard base calc'd.: 285.3; found: 283.3.

2-Phenyl-3-oxo-4-isoindolinecarboxylic Acid (VII)

A mixture of V (1.0 g., 3.7 mmole) in 15.0 ml. of glacial acetic acid and 2.0 ml. of sulfuric acid was heated at 60—65° for 30 minutes, cooled, diluted with water and filtered. The crude product VII (0.53 g., 56%, m. p. 216—217°) was recrystallized from ethanol with the aid of decolorizing charcoal. Further recrystallizations from ethanol afforded colourless needles, m. p. 219—220°.

Anal. C₁₅H₁₁NO₃ (253.26) calc'd.: C 71.14, H 4.38, N 5.53%
found: C 71.05, H 4.70, N 5.46%

2-p-Tolyl-3-oxo-4-isoindolinecarboxylic Acid (VIII)

It was obtained in the same manner as described for VII. From VI (1.0 g., 3.5 mmole), 0.65 g. (70%) of VIII, m. p. 209—210° was obtained. After recrystallizations from ethanol (charcoal) colourless needles, m. p. 215—216°.

Anal. C₁₆H₁₃NO₃ (267.29) calc'd.: C 71.90, H 4.90, N 5.24%
found: C 71.91, H 4.63, N 5.05%

Decarboxylation of VII

0.37 g. (1.46 mmole) of VII, 2.5 ml. of quinoline and 0.37 g. of copper-powder were placed in a conical flask (25 ml.) equipped with a small air condenser. The mixture was heated under reflux about 8 minutes. After addition of small portion of ether the suspension was filtered off. To effect precipitation, petroleum ether (40—60°) was added to the filtrate, yielding 0.128 g. (42%) of *N*-phenylphthalimidine (IX), m. p. 159—160°. After recrystallization from ethanol (charcoal) it melted at 163—164°. The infrared spectrum was identical with the infrared spectrum of an authentic sample prepared by the method of Thiele and Schneider⁴. Mixed m. p. 163—164°. (Lit.⁴ m. p. 161°).

Decarboxylation of VIII

Decarboxylation of 2-*p*-tolyl-3-oxo-4-isoindolinecarboxylic acid (VIII) was carried out in the same manner as for 2-phenyl analogue VII, and a 34% yield of crude *N*-*p*-tolylphthalimidine (X), m. p. 135—136°, was obtained. It was purified by crystallizations from ethanol (charcoal) to give pure X, m. p. 140°. An authentic sample of this material was prepared from *o*-phthalaldehyde and *p*-toluidine in a similar way as described for *N*-phenylphthalimidine⁴. The infrared spectra of two materials were superimposable and the melting point of their mixture was 140°. (Lit.⁵ m. p. 140°).

Me 2-phenyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylate (XI)

The solution of V (0.2 g., 0.74 mmole), absolute methanol (10.0 ml.) and sulfuric acid (1.0 ml.) was allowed to stand at room temperature for 1 hr. and then evaporated *in vacuo* to a small volume. The ester XI was precipitated by adding 15.0 ml. of water and a solution of sodium hydroxide (20%) until the solution was slightly alkaline. The yield was 0.134 g. (64%); m. p. 126—127°. The substance was recrystallized from methanol, colourless needles m. p. 128—129°.

Anal. C₁₆H₁₅NO₄ (285.30) calc'd.: C 67.36, H 5.30, N 4.91%
found: C 67.62, H 5.49, N 5.14%

The ester XI was treated in ethanol with cold 20% sodium hydroxide for 3 hrs. Acidification then precipitated acid V, m. p. and mixed m. p. 184—185°.

Me 2-p-tolyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylate (XII)

The substance was prepared by the method described for ester XI in yield of 81%. Colourless needles from methanol, m. p. 175—176°.

Anal. $C_{17}H_{17}NO_4$ (299.33) calc'd.: C 68.22, H 5.72, N 4.68%
found: C 68.46, H 5.72, N 4.60%

Saponification of this ester gave acid VI, m. p. and mixed m. p. 182—184°.

N-(2-furfuryl)-isomaleimide (XIV)

A mixture of *N*-furfurylmaleamic acid, m. p. 114°, (XIII)⁶ (0.6 g., 3.1 mmole), 1.5 ml. of acetic anhydride and 0.14 g. of anhydrous sodium acetate was kept at room temperature for 4 hrs. and then 35.0 ml. of water was added. The precipitate XIV was washed with sodium bicarbonate (5%) and water; 0.4 g. (73%), m. p. 99—100°. From ethanol colourless needles m. p. 101—102°. The infrared absorptions (potassium bromide): 1795 cm^{-1} (5-lactone) and 1690 cm^{-1} (C = N).

Anal. $C_9H_7NO_3$ (177.16) calc'd.: C 61.02, H 3.98, N 7.91%
found: C 60.73, H 4.25, N 7.68%

2-Methyl-3-oxo-4-isoindolinecarboxylic Acid (XVI)

A mixture of 2-methyl-3-oxo-5,7a-epoxy-3a,4,5,7a-tetrahydro-4-isoindolinecarboxylic acid, m. p. 172—173° (XV)* (0.5 g., 2.4 mmole) and 1.9 ml. of dilute sulfuric acid (4 : 1) was heated at 60° for 15 minutes, cooled, diluted with water (5.0 ml.) and filtered. The crude product XVI (0.31 g., 67%, m. p. 197—199°) was recrystallized from ethanol with the aid of decolorizing charcoal. Two further recrystallizations from ethanol gave colourless needles, m. p. 203—204°.

Anal. $C_{10}H_9NO_3$ (191.19) calc'd.: C 62.82, H 4.74, N 7.33%
found: C 63.01, H 4.89, N 7.47%

Decarboxylation of XVI

0.3 g. (1.6 mmole) of XVI, 1.5 ml. of quinoline and 0.3 g. of copper-powder were heated under reflux for 40 minutes. The solution was extracted with water. After standing overnight water was allowed to evaporate and the resulting solid of *N*-methylphthalimidine (XVII) after recrystallization from ether melted at 114—115°. Yield 0.025 g. (11%). The sample gave no depression of melting point in a mixture with an authentic sample prepared by the already described method⁸. (Lit.⁸ m. p. 114.5—115.5°). The infrared spectra were superimposable.

Acknowledgments. The technical assistance of Miss M. Momčilović is gratefully acknowledged. Thanks also are due to Mrs. J. Zake and Mrs. A. Tkalac for the microanalyses here reported.

REFERENCES

1. D. Bilović, Ž. Stojanac, and V. Hahn, *Tetrahedron Letters* **1964**, 2071.
2. N. B. Mehta, A. P. Phillips, F. F. Lui, and R. E. Brooks, *J. Org. Chem.* **25** (1960) 1012.
3. V. Hahn, R. Hansal, I. Markovčić, and D. Vargazon, *Arhiv Kem.* **26** (1954) 21.
4. J. Thiele and J. Schneider, *Ann.* **369** (1909) 287; cit. from *Chem. Zentr.* **1909**. II. 2167.
5. D. H. Peacock, *J. Chem. Soc.* **1951**, 891.
6. W. Herz, *J. Am. Chem. Soc.* **67** (1945) 2272.
7. A. H. J. Cross, S. G. E. Stevens, and T. H. E. Watts, *J. Appl. Chem.* **7** (1937) 562.
8. J. H. Brewster, A. M. Fusco, L. E. Carosino, and B. G. Corman, *J. Org. Chem.* **28** (1963) 498.

* Prepared from furfurylmethylamine and maleic anhydride in ether according to the method of Herz⁶, who reported this compound as *N,N*-furfurylmethylmaleamic acid.

IZVOD**Reakcija arilfurfurilamina sa anhidridom maleinske kiseline***D. Bilović*

Opisana je reakcija (2-furfuril)-anilina (I) i (2-furfuril)-*p*-toluidina (II) sa anhidridom maleinske kiseline. Utvrđeno je da tom reakcijom nastaju 2-fenil-3-okso-5,7a-epoksi-3a,4,5,7a-tetrahidro-4-izoindolinkarbonska kiselina (V) i 2-*p*-tolil-3-okso-5,7a-epoksi-3a,4,5,7a-tetrahidro-4-izoindolinkarbonska kiselina (VI).

Pretpostavlja se, da su ti produkti dobiveni preko intermedijarnih *N,N*-arilfurfurilmaleaminskih kiselina (III) i (IV) intramolekularnom Diels-Alder-ovom reakcijom.

INSTITUT »RUĐER BOSKOVIĆ«
ZAGREB

Primljeno 10. lipnja 1966.