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Original Scientific Paper

exo-endo Isomerization in an Intramolecular Diels-Alder Reaction

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The isomerization of 2-phenyl-3-oxo-5,7*a*-epoxy-3*a*,4,5,7*a*-tetrahydro-4-isoindolinecarboxylic acid (II) and 2-*p*-tolyl-3-oxo-5,7*a*-epoxy-3*a*,4,5,7*a*-tetrahydro-4-isoindolinecarboxylic acid (III) derived from the reaction of arylfurfurylamines and maleic anhydride was investigated. On the basis of iodolactone formation, *endo* carboxyl configuration was assigned to the rearranged products, while *exo* configuration was assigned for the starting materials. The NMR data support these assignments.

In a recent publication[1] the isolation of 2-phenyl-3-oxo-5,7*a*-epoxy-3*a*,4,5,7*a*-tetrahydro-4-isoindolinecarboxylic acid (II) and 2-*p*-tolyl-3-oxo-5,7*a*-epoxy-3*a*,4,5,7*a*-tetrahydro-4-isoindolinecarboxylic acid (III) from a reaction of the corresponding arylfurfurylamines with maleic anhydride in ethanol was reported.The suggestion was made that the reaction proceeded *via* the intermediate formation of *N,N*-arylfurfurylmaleamic acids followed by an intramolecular Diels-Alder reaction.

In the present paper further chemical and spectroscopic evidence supporting the validity of the proposed reaction pathway is presented along with new additional data characterizing more completely the products of the internal diene addition.

When the reaction of (2-furfuryl)-aniline[2] with maleic anhydride was performed at room temperature without solvent, the intermediate *N,N*-furfurylphenylmaleamic acid (I) could be obtained as a white solid. Its structure was confirmed by elemental analysis and by its infrared spectrum (Fig. 1), which differed from the spectrum of II and showed a maximum at 1020 cm^{-1} characteristic for a furan nucleus[3]. It was shown that I, when heated at 115° for a short period of time, was unstable giving the cyclic product II. Maleamic acid I is very soluble in ethanol and this solution deposits spontaneously II.

The behavior of I upon heating and storage in ethanol can be readily explained by the fact that it possesses a dienic and dienophilic part which enable isomerization of I to II by an intramolecular Diels Alder reaction.

The reaction of a cyclic diene with a dienophile can afford either *endo* or *exo*[4] products which can often interconvert[5]. Thus, when II m. p. 184—185°, was heated in a mixture of pyridine and glacial acetic acid (1 : 1), a compound V m. p. 191—192° was formed. This product was shown to be an isomer of II. It has the same elemental composition as II, titration with standard base indicated the presence of one acidic hydrogen and when treated with dilute sulfuric acid, 2-phenyl-3-oxo-4-isoindolinecarboxylic acid (VIII) was obtained. VIII was proved to be identical with the dehydration product of II[1].

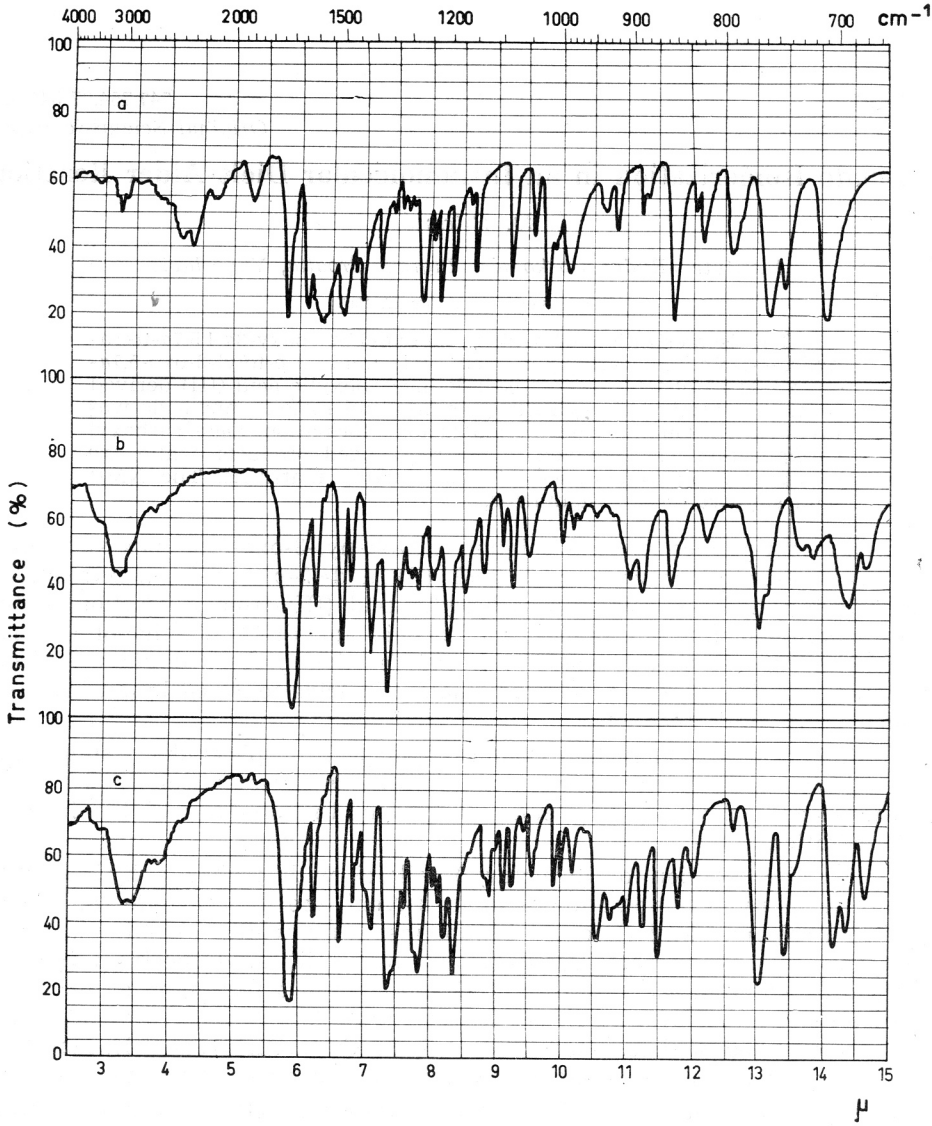
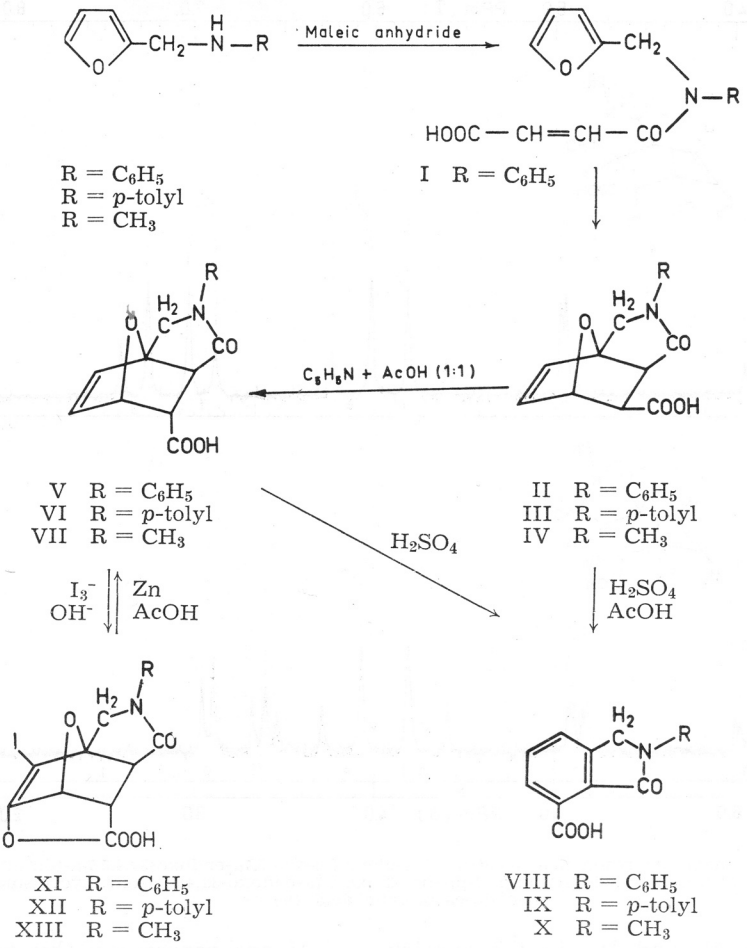


Fig. 1. Infrared absorption spectra: a) maleamic acid I; b) *exo*-acid II; c) *endo*-acid V.

The reaction of the higher melting isomer V with iodine-potassium iodide solution in dilute sodium hydroxide-sodium bicarbonate solution[6] gave the iodolactone XI in a good yield. From this iodolactone the pure acid V was regenerated by zinc-acetic acid reduction[7]. The starting acid II proved to be inert to aqueous iodine solution and could be readily recovered in pure form. Since only the higher melting isomer V gave an iodolactone it is possible to conclude that V has the *endo* carboxyl configuration, while II is the *exo* isomer.



III and 2-methyl-3-oxo-5,7*a*-epoxy-3*a*,4,5,7*a*-tetrahydro-4-isoindolinecarboxylic acid (IV)[1] behaved identically as II yielding *endo*-acid VI and *endo*-acid VII respectively. Owing to the lack of iodolactone formation, *exo* configurations are assigned to III and IV.

endo-Acids V and VI could easily be esterified in absolute methanol in the presence of sulfuric acid, giving the corresponding methyl-esters, which upon saponification yielded the starting acids V and VI, respectively.

NMR Assignments

The proton NMR spectra strongly support the proposed structures for compounds II and V.

The nonequivalent geminal protons H_d and H_e appeared as a quartet of an AB system, and vinyl protons H_a and H_b as multiplet in which the proton H_b is coupled with bridghead proton H_c (Fig 2, Table I).

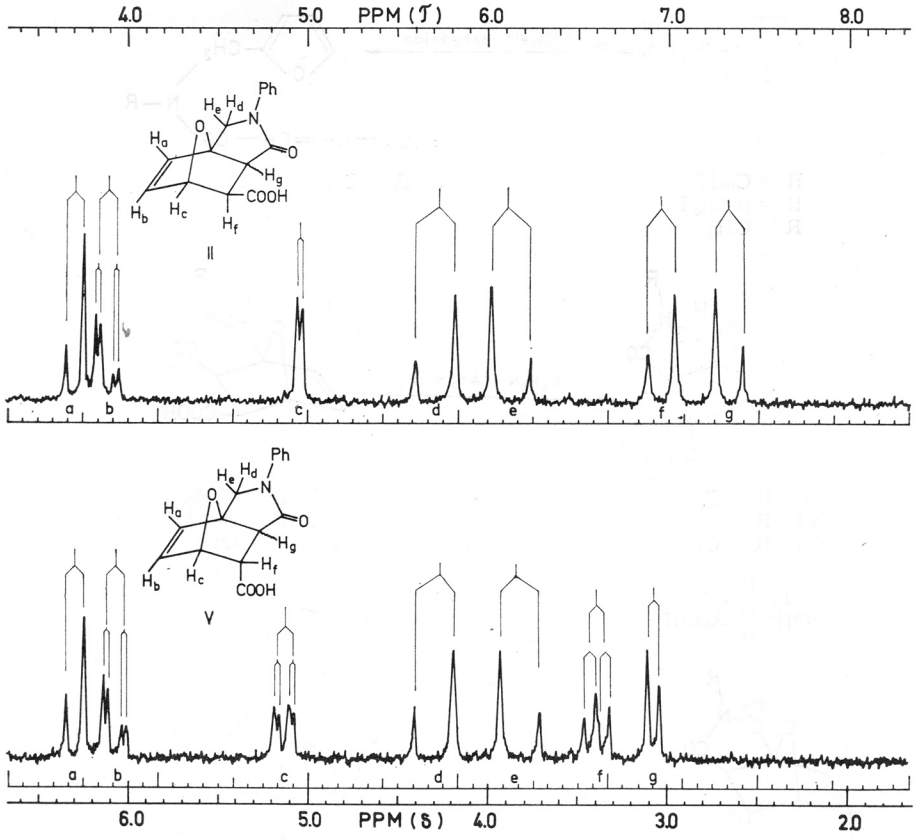


Fig. 2. Proton magnetic resonance spectra of 2-phenyl-3-oxo-5,7*a*-endoxo-3*a*,4,5,7*a*,-tetrahydroisoindoline-4-*exo*-carboxylic acid (II) and 2-phenyl-3-oxo-5,7*a*-endoxo-3*a*,4,5,7*a*-tetrahydroisoindoline-4-*endo*-carboxylic acid (V)

Protons H_f and H_g in the spectrum of II are represented by an AB quartet with J_{fg} 9.0 c.p.s. No appreciable coupling takes place between H_f and bridghead proton H_c*.

In the spectrum of the *endo*-acid V the quartet centered at τ 6.61 is attributed to the proton H_f coupled by 3.5 and 5.0 c.p.s. with protons H_g and H_c respectively*.

The large coupling constant J_{fg} 9.0 c.p.s. for *exo*-acid II, indicates that the stereochemistry of H_g in the *exo*-acid may be *endo*.[8,9] The corresponding coupling constant J_{fg} 3.5 c.p.s. for *endo*-acid V indicates a dihedral angle of about 120°[8]. Though these data and molecular models are fairly in agreement, the full elucidation of structural relationship of the proton H_g will be published later after additional elaboration which is in progress.

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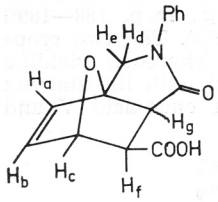
* These data are in full agreement with the Karplus[8] correlation of spin-spin coupling constants with dihedral angles; according to models the relevant dihedral angles $H_c—C_5—C_4—H_f$ are cca 90° for II corresponding to $J \cong 0$, and cca 40° for V corresponding to $J \cong 5.0$ c. p. s.

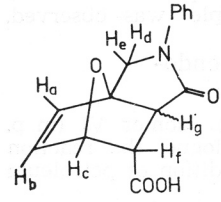
TABLE I

NMR Spectra of exo-*Acid II and* endo-*Acid V at 60 Mc.*[a] *Hydrogen Assignment*



	a	b	c	d*	e*	f	g	Ph
1)	3.70	3.90	4.98	5.72	6.12	6.97	7.33	3.07
2)	J_{ab}6.0			J_{de}13.0		J_{fg}9.0		
	J_{bc}1.5							
3)	—— 2 H ——		1 H	—— 2 H ——		—— 2 H ——		5 H

II



	a	b	c	d*	e*	f	g	Ph
1)	3.70	3.93	4.88	5.72	6.16	6.61	6.94	3.07
2)	J_{ab}6.0		J_{cf}5.0	J_{de}13.0		J_{fg}3.5		
	J_{bc}1.5							
3)	—— 2 H ——		1 H	—— 2 H ——		1 H	1 H	5 H

V

[a] The data are listed for each hydrogen: 1) Chemical shift in CF_3COOH relative to TMS (10.0τ). 2) Coupling constants in c.p.s. 3) Integrated relative areas.
* The position can be assigned to the d and e protons but not specifically to one or the other.

EXPERIMENTAL

All melting points are uncorrected.

N,N-*Furfurylphenylmaleamic Acid* (I)

Finely powdered maleic anhydride (28.0 mg., 0.286 mmole) was dissolved in freshly distilled (2-furfuryl)-aniline[2] (110 mg., 0.636 mmole). The solution deposited maleamic acid I upon standing and some scratching. The solid separated by spreading on ceramic plate, repeatedly washed by ether. Yield: 27 mg. (35%). Infrared absorption spectrum (KBr plates), quite different from that of acid II previously obtained from the same components in ethanol[1], is shown in Fig. 1.

Anal. $C_{15}H_{13}NO_4$ (271.28) calc'd.: C 66.41; H 4.83; N 5.16%
found: C 66.52; H 5.13; N 5.32%

The white powder of maleamic acid I softened slightly at about 88° and melted completely at 179—180°. If placed in preheated melting point apparatus at 115° it melted into a clear liquid which resolidified at once. Final m. p. 179—180°. The product of m. p. 179—180° (capillary tube), 184—185° (Koffler heating microscope) was proved to be identical with II by admixture with the pure acid[1].

Maleamic acid I is very soluble in ethanol. The ethanolic solution deposited spontaneously after a few minutes acid II.

2-*Phenyl-3-oxo-5,7a-endoxo-3a,4,5,7a-tetrahydroisoindoline-4-endo-carboxylic Acid* (V)

exo-Acid II (m. p. 184—185°)[1] (1.0 g., 3.686 mmole) and 2.0 ml. of a mixture of pyridine and glacial acetic acid (1 : 1) were heated in an oil bath (145 ± 1°) for 30 minutes. After cooling the dark brown solution was shaken with 3.0 ml. of petroleum ether (30—40°) and left at room temperature for 2 days. During this period *endo*-acid V gradually settled out. The obtained crystalline material (0.156 g.,

m. p. 187—188°) was filtered and washed with acetic acid. The filtrate and the washings were combined and the solvent evaporated *in vacuo*. The dark semi-solid brown residue was dissolved in 1.0 ml. of glacial acetic acid and left to stand overnight. In this way a second crop of crystals of V (0.186 g., m. p. 188—189°) was obtained. The total yield of crude *endo*-acid was 0.34 g. (34%). The two crops of crystals were combined and recrystallized from acetic acid (charcoal) yielding colorless crystals m. p. 191—192°. Mixed melting point of this acid with the starting *exo*-acid II was 163—167°. The infrared spectra (KBr plates) of *endo*-acid V and *exo*-acid II are shown in Fig. 1.

Anal. $C_{15}H_{13}NO_4$ (271.28) calc'd.: C 66.41; H 4.83; N 5.16%
found: C 66.07; H 5.06; N 5.18%

Neutralization equivalent by titration with standard base calc'd.: 271.38; found 270.05

A mixture of V (0.1 g., 0.368 mmole) and 1 ml. of dilute sulfuric acid (4 : 1) was heated at 60° for 15 minutes, cooled, diluted with water (4 ml.) and filtered. The resulting crude 2-phenyl-3-oxo-4-isoindolinecarboxylic acid (VIII) (0.080 g., 86% m. p. 204—208°) was recrystallized from ethanol (charcoal), m. p. 219—220°. No melting point depression on admixture with the original sample[1] was observed.

2-p-Tolyl-3-oxo-5,7a-endoxo-3a,4,5,7a-tetrahydroisoindoline-4-endo--carboxylic Acid (VI)

exo-Acid III (m. p. 183—184°)[1] was transformed to the *endo* isomer VI (m. p. 216—217°, yield 46%) in the similar way as the *N*-phenyl analogue, the reaction mixture being left overnight at room temperature without the addition of petroleum ether. M. p. 219—220° (from acetic acid).

Anal. $C_{16}H_{15}NO_4$ (285.30) calc'd.: C 67.36; H 5.30; N 4.91%
found: C 67.48; H 5.25; N 5.08%

Neutralization equivalent by titration with standard base calc'd.: 285.30; found: 284.00. Dehydration of VI by sulfuric acid performed in the same way as that of *N*-phenyl analogue V, gave 2-*p*-tolyl-3-oxo-4-isoindolinecarboxylic acid (IX)[1] in 62% yield.

2-Methyl-3-oxo-5,7a-endoxo-3a,4,5,7a-tetrahydroisoindoline-4-endo--carboxylic Acid (VII)

When 2-methyl-3-oxo-5,7*a*-endoxo-3*a*,4,5,7*a*-tetrahydroisoindoline-4-*exo*-carboxylic acid (IV) (m. p. 172—173°)[1] was treated in the same way as III (but heating prolonged to 40 minutes) it isomerized to the *endo* isomer VII (m. p. 196—197°, yield 48%). On recrystallization from acetic acid it melted at 202—203°.

Anal. $C_{10}H_{11}NO_4$ (209.21) calc'd.: C 57.41; H 5.30; N 6.70%
found: C 57.13; H 5.49; N 7.04%

Neutralization equivalent by titration with standard base, calc'd.: 209.21; found: 208.56. Sulfuric acid dehydration of VII gave 2-methyl-3-oxo-4-isoindolinecarboxylic acid (X)[1] in 58% yield.

Iodolactone XI*

endo-Acid V (0.4 g., 1.475 mmole) in 3 ml. of water was almost neutralized with a 10% sodium hydroxide solution and 60 mg. sodium hydrogen carbonate was added. The clear solution was treated with 2.5 ml. of an iodine solution prepared from 5.0 g. of iodine, 10 g. of potassium iodide and 30.0 ml. of water, over a period of 30 minutes with occasional swirling. The remaining iodine was destroyed with a few ml. of aqueous sodium thiosulfate, the white tan iodolactone XI filtered off and washed with water. The yield 0.45 g. (77%). XI was purified by crystallization from pyridine. It melted with extensive decomposition when put into a bath at 295°. The material was insoluble in 10% bicarbonate solution. The carbonyl absorption maximum occurred at 1805 cm^{-1} (Nujol mull)[10].

Anal. $C_{15}H_{12}INO_4$ (397.18) calc'd.: C 45.36; H 3.05; N 3.53; I 31.95%
found: C 45.23; H 2.99; N 3.84; I 31.99%

Regeneration of endo-*Acid V from Iodolactone* XI

To iodolactone XI (0.3 g., 0.755 mmole) and 12.0 ml. of glacial acetic acid 0.4 g. of zinc dust was added. The mixture was stirred for one hour. Two additional portions of zinc (0.4 g. each) were added, the mixture being stirred after each addition for one hour. Zinc was removed by filtration and then washed well with acetic acid. Acetic acid was removed *in vacuo*. To the crystalline residue 15 ml. of water and one drop of hydrochloric acid were added. After filtration and washing with acetic acid 0.114 g. of *endo*-acid V, m. p. 187—188° was obtained. An additional crop of the crystals (0.02 g.) of the same melting point was obtained by boiling zinc cake with acetic acid and working up in the same manner as the main fraction. Total yield 0.134 g. (65%). The two crops of the crystals were combined and recrystallized once more from acetic acid giving analytical sample which melted at 191—192°. Mixed melting point with pure *endo*-acid V was undepressed.

Iodolactone XII*

It was prepared from *endo*-acid VI as described for XI. The yield of crude iodolactone XII (m. p. 266°) was 89%. After recrystallization from pyridine it melted at 278° (decomp.). The material was insoluble in 10% bicarbonate solution. The carbonyl absorption maximum observed at 1.802 cm^{-1} (Nujol mull)[10].

Anal. $C_{16}H_{14}INO_4$ (411.21) calc'd.: C 46.74; H 3.43; N 3.41; I 30.86%
found: C 46.67; H 3.48; N 3.46; I 30.80%

The iodolactone XII was reductively cleaved by zinc as described for iodolactone XI. The pure endo-acid VI was obtained in 70% yield.

Iodolactone XIII*

Prepared as described for XI from *endo*-acid VII in 47% yield. M. p. of crude iodolactone was 242—243°. After recrystallization from pyridine it melted at 244—245° (decomp.). XIII was insoluble in 10% bicarbonate solution. The carbonyl absorption maximum exhibited a band at 1783 cm^{-1} (Nujol mull)[10].

Anal. $C_{10}H_{10}INO_4$ (335.11) calc'd.: C 35.84; H 3.01; N 4.18; I 37.87%
found: C 35.74; H 3.39; N 4.50; I 38.04%

The pure *endo*-acid VII was obtained by reductive cleavage of XIII with zinc and acetic acid.

*Methyl 2-phenyl-3-oxo-5,7a-endoxo-3a,4,5,7a-tetrahydroisoindoline-4-*endo-*-carboxylate* (XIV)

This ester was prepared in the same way as its *exo*-isomer (see ref. 1., compound XI) from acid V and absolute methanol in the presence of sulfuric acid in 68% yield. Colorless needles from methanol, m. p. 129—130°.

Anal. $C_{16}H_{15}NO_4$ (285.30) calc'd.: C 67.36; H 5.30; N 4.91%
found: C 67.22; H 5.72; N 4.78%

*Methyl 2-*p*-tolyl-3-oxo-5,7a-endoxo-3a,4,5,7a-tetrahydroisoindoline-4-*endo-*-carboxylate* (XV)

It was prepared in 83% yield from acid VI and absolute methanol and sulfuric acid in the manner described for its *exo* isomer (see ref. 1., compound XII). Colorless needles m. p. 144—145° after recrystallization from methanol.

Anal. $C_{17}H_{17}NO_4$ (299.33) calc'd.: C 68.21; H 5.72; N 4.68%
found: C 67.91; H 5.68; N 4.84%

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* The *endo* acids V, VI and VII (0.37 mmole of each) used up 95—97% of the calculated amount of iodine stock solution. When *exo*-acids II, III and IV were similarly treated with a small amount of iodine stock solution no discharge of color occurred and acidification precipitated the unchanged starting acids.

The esters XIV and XV were hydrolyzed with methanolic potassium hydroxide (10%) for 1 hr. at 50°, and an aqueous solution of the potassium salt neutralized with HCl to yield *endo*-acid V and *endo*-acid VI, respectively.

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IZVOD

Egzo-endo Izomerizacija u intramolekularnoj Diels-Alderovoj reakciji

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Nađeno je da 2-fenil-3-okso-5,7*a*-epoksi-3*a*,4,5,7*a*-tetrahidro-4-izoindolinkarbonska kiselina (II) i 2-*p*-tolil-3-okso-5,7*a*-epoksi-3*a*,4,5,7*a*-tetrahidro-4-izoindolinkarbonska kiselina (III)[1] zagrijavanjem u smjesi piridin-octena kiselina (1 : 1) izomeriziraju u spojeve višeg tališta V i VI. Na temelju stvaranja jodolaktona pripisuje se *endo* karboksil konfiguracija izomernim produktima (V i VI), dok se polaznim tvarima (II i III) pripisuje *egzo* karboksil konfiguracija. Proton NMR spektri produkta II i njegovog *endo* izomera V u potpunom su skladu s predloženim strukturama.

Ranije[1] je dana pretpostavka da su spojevi II i III dobiveni iz reakcije odgovarajućih arilfurfurilamina s anhidridom maleinske kiseline preko intermedijera *N*,*N*-arilfurfurilmaleaminske kiseline intramolekularnom Diels-Alderovom reakcijom. U ovom radu prikazana je izolacija i osebine intermedijera *N*,*N*-fenilfurfurilmaleaminske kiseline (I).

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ZAGREB

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