

CCA-1171

YU ISSN 0011-1643

547.23.24

Original Scientific Paper

Reactions with 5-Arylazo- and 5-Arylidene-4-thiohydantoin Derivatives

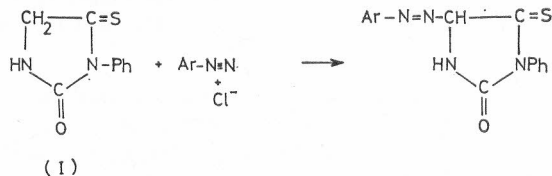
A. F. A. Shalaby, M. A. Abdel Aziz, and M. A. Abd Allah

Chemistry Department, Faculty of Science, Cairo University, Giza-Egypt

Received April 5, 1979

5-Arylazo-3-phenyl-4-thiohydantoin (IIa-g) have been prepared and then treated with primary aromatic amines to afford the corresponding 5-arylazo-4-arylimino-3-phenyl hydantoins (VIIa-c). 3-Phenyl-4-thiohydantoin reacted with aromatic aldehydes in the presence of glacial acetic acid and fused sodium acetate to give 5-arylidene-3-phenyl-4-thiohydantoin derivatives (VIIIa-e). In the coloured arylidene derivatives (VIII, a d, e) on treatment with alkyl- and/or arylmagnesium halide addition occurs to the exocyclic double bond to give the products (IXa-e). The Grignard product (Xa) was oxidised with a mixture of chromic acid in glacial acetic acid to give phenyl parabanic acid and ethyl phenyl ketone.

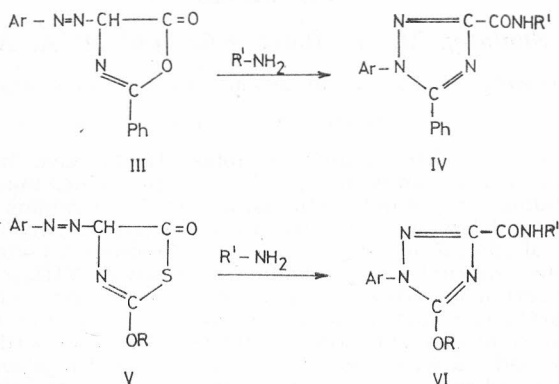
5-Membered heterocyclic compounds containing a methylene group adjacent to a carbonyl group couple with aromatic diazonium compounds to give the corresponding azo derivatives.¹⁻³ Although 5-substituted hydantoins have found use in medicine as hypnotics and others are used as essential medicinal products having a wide application, yet little is known about 5-arylazo thiohydantoins and till now the coupling of the diazonium salts with hydantoin and its derivatives is unknown. 4-Thiohydantoin was prepared by refluxing hydantoin with phosphorous pentasulphide in dioxane⁴. In this Laboratory 3-phenyl-hydantoin was prepared by the condensation of glycine with phenyl isocyanate in alkaline medium followed by cyclization of the product with concentrated hydrochloric acid. The product when refluxed with phosphorous pentasulphide in dioxane gave 3-phenyl-4-thiohydantoin (I) in good yield. The new arylazo derivatives (IIa-g) needed for this investigation were prepared according to the procedure described by Baranov⁵.



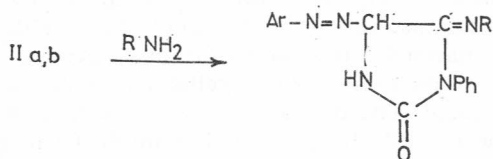
- IIa, Ar = C₆H₅
 b, Ar = *m*-CH₃C₆H₄
 c, Ar = *p*-CH₃C₆H₄
 d, Ar = *p*-ClC₆H₄
 e, Ar = *p*-SO₃HC₆H₄
 f, Ar = *o*-NO₂C₆H₄
 g, Ar = β-naphthyl

The 5-arylozo-3-phenyl-4-thiodydantoin (IIa-g) are red and gave the correct analytical data.

It has been reported that in 5-arylozo-2-phenyl oxazolin-5-ones (III), when treated with aromatic amines in methanol, opening of the azlactone ring occurs followed by cyclization to give the anilides of 1-aryl-5-phenyl-1H-1,2,4-triazole-3-carboxylic acids (IV)⁶. Mustafa et al.⁷ reported that 4-arylozo-2-alkoxy-2-thiazolin-5-ones (V) reacted with aromatic amines to yield *N*-arylamide of 5-alkoxy-1H-1,2,4-triazole-3-carboxylic acid (VI). Contrast to these

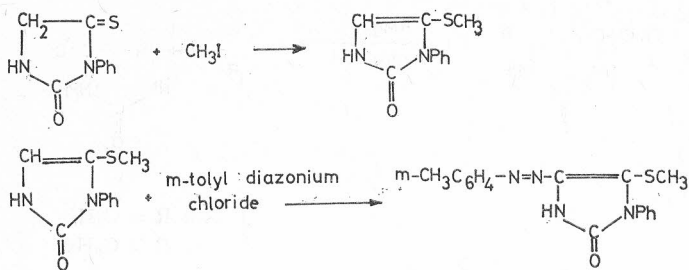


examples the thiohydantoin ring appeared to be stable toward aromatic amines as was shown when the coloured 5-arylozo-3-phenyl-4-thiohydantoin (IIa, b) were fused with primary aromatic amines in an oil bath (150–160 °C) until dissolution occurred and no odour of hydrogen sulphide could be detected, precipitating 5-arylozo-3-phenyl-4-arylimino hydantoin derivatives (VIIa-c).

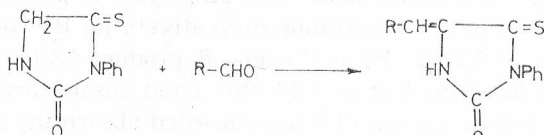


- VIIa, Ar = R = C₆H₅
 b, Ar = *m*-CH₃C₆H₄; R = C₆H₅
 c, Ar = R = *m*-CH₃C₆H₄

Compounds VIIa-c gave the correct analytical values and their structure was confirmed when IIb was treated with methyl iodide affording 5-(*m*-tolylazo)-3-phenyl-4-methylmercapto hydantoin which, on treatment with aniline gave VIIb in good yield. Also 3-phenyl-4-thiohydantoin was methylated with methyl iodide in the presence of alcoholic sodium hydroxide to give the corresponding methylmercapto derivative. This last product was treated with a cold *m*-tolyl diazonium chloride solution and the expected product was separated. It was identified as 5-(*m*-tolylazo)-3-phenyl-4-methylmercaptohydantoin by melting point and mixed melting point determinations (cf. Scheme A).

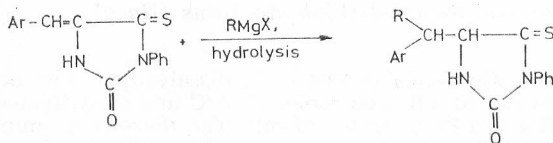


It was first shown by Wheeler and Hoffmann⁸ that hydantoin condensed with aromatic aldehydes to give C-5 unsaturated hydantoin derivatives. Also 2-thiohydantoin underwent condensation with aromatic aldehydes more easily than the corresponding oxygen hydantoin^{9,10}. Similarly, 3-phenyl-4-thiohydantoin reacted with aromatic aldehydes in boiling glacial acetic acid and in the presence of fused sodium acetate to give the corresponding arylidene derivatives (VIIIa-e) in good yields. The 5-arylidene-3-phenyl-4-thiohydantoin (VIIIa-e) are all coloured compounds.

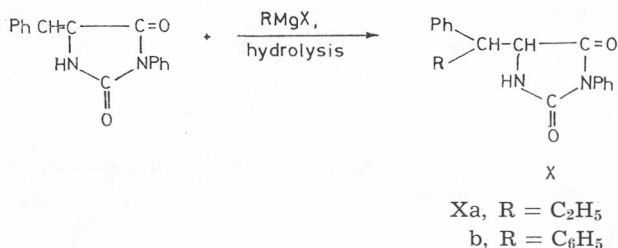


- VIIIa, R = C₆H₅
 b, R = *m*-NO₂C₆H₄
 c, R = *p*-CH₃OC₆H₄
 d, R = 2,4-Cl₂C₆H₃
 e, R = *p*-N(CH₃)₂C₆H₄

Addition of organomagnesium compounds to the exocyclic double bond of a heterocyclic nitrogen ring having a carbonyl function has been reported in the literature¹¹⁻¹⁴. This study was extended to the behaviour of Grignard reagents on the new 5-arylidene-3-phenyl-4-thiohydantoin (VIIIa, d, e) having an exocyclic double bond conjugated with the thione group. Thus, when the coloured compounds (VIIIa, d, e) were treated with Grignard reagents followed by hydrolysis, the corresponding colourless products (IXa-e) were obtained. The structure of the obtained products was inferred from the fact that: (1) They gave the correct analytical values. (2) IXa was synthesised by another method: 5-benzylidene-3-phenyl hydantoin was treated with ethylmagnesium iodide followed by hydrolysis to give Xa which on treatment with phosphorous pentasulphide in dioxane gave IXa (bath temp. 130-140 °C). Similarly, 5-



- IXa, Ar = C₆H₅; R = CH₃CH₂
 b, Ar = R = C₆H₅
 c, Ar = 2,4-Cl₂C₆H₃; R = *p*-CH₃C₆H₄
 d, Ar = 2,4-Cl₂C₆H₃; R = CH₃CH₂
 e, Ar = *p*-N(CH₃)₂C₆H₄; R = CH₃CH₂



-benzylidene-3-phenyl hydantoin was treated with phenylmagnesium bromide to give Xb in good yield. (3) 3-Phenyl-4-thiohydantoin proved to be stable towards the action of phenylmagnesium bromide under similar experimental conditions; thus showing the stability of the thiohydantoin ring towards the action of Grignard reagents. (4) In addition to the above facts, when the product Xa was oxidised with a mixture of chromic acid in glacial acetic acid the molecule was cleared at the connection of the exocyclic chain with the heterocyclic ring to give phenyl parabanic acid¹⁵ and ethyl phenyl ketone which was identified by its 2,4-dinitrophenylhydrazone derivative¹⁶. (5) By comparing the UV absorption spectra of VIIIId and its Grignard product IXd, it was found that VIIIId absorbs at 336 nm, but in IXd this band disappeared. Also, the measurement of the infrared spectra of VIIIa recorded absorption at 1625 cm⁻¹, but this band was not shown in the corresponding Grignard product; these facts confirmed that the conjugation had been interrupted and saturation occurred.

EXPERIMENTAL

Action of Phosphorous Pentasulphide on 3-Phenylthiohydantoin (I)

17.6 g (0.1 mol) of 3-phenyl hydantoin were mixed well with 9 g phosphorous pentasulphide and covered with 100 ml of dry dioxane (dried over potassium hydroxide, and then over metallic sodium). The reaction mixture was refluxed for 40 minutes at 115–120 °C (bath temperature). When the reaction was completed, 1 g of zinc dust and 0.5 g of charcoal were added to the solution and the heating was continued for five more minutes. The hot solution was filtered, concentrated to half its volume and then poured over ice-cold water. The solid separated was collected and recrystallized from absolute ethyl alcohol to give 11.5 g (82% yield) of 3-phenyl-4-thiohydantoin (m. p. 221 °C) as yellow crystals.

Anal. C₉H₈N₂OS calc'd.: C 56.25; H 4.17; N 14.58; S 16.67%
found: C 56.1; H 4.1; N 14.6; S 16.7 %

Preparation of 5-Arylazo-3-phenyl-4-thiohydantoin (IIa-g)

General Procedure

The appropriate aromatic amine (0.0068 mol), dissolved in concentrated hydrochloric acid (6 ml) and water (6 ml), was cooled to 0 °C and then treated with a cold solution of sodium nitrite (0.6 g) in water (6 ml). The diazotized amine was added gradually to an ice-cold solution of 1.3 g 3-phenyl-4-thiohydantoin dissolved in 40 ml of 2% sodium hydroxide solution. After the addition was completed, the reaction mixture was left to stand in a cold chest for 1 hour. The product separated was filtered off, washed with water and crystallized from acetic acid (cf. Table I). All the obtained 5-arylazo-3-phenyl-4-thiohydantoin derivatives are red colour and are sparingly soluble in sodium hydroxide solution.

TABLE I
5-Arylazo-3-phenyl-4-thiohydantoin (IIa-g)

	M. P. °C	Yield %	Formula	Analysis		Calc'd	S/%
				C/%	H/%	Found N/%	
IIa	270	85	C ₁₅ H ₁₂ N ₄ OS	60.81 60.9	4.05 4.0	18.92 19.0	10.81 10.9
b	255	80	C ₁₆ H ₁₄ N ₄ OS	61.94 61.9	4.52 4.6	18.06 18.0	10.32 10.4
c	217	78	C ₁₆ H ₁₄ N ₄ OS	61.94 62.0	4.52 4.5	18.06 18.1	10.32 10.3
d	259	80	C ₁₅ H ₁₁ N ₄ OSCI*	54.46 54.5	3.33 3.4	16.94 17.0	9.68 9.7
e	265	82	C ₁₅ H ₁₂ N ₄ O ₄ S	47.87 47.9	3.19 3.2	14.89 14.9	17.02 17.0
f	261	65	C ₁₅ H ₁₁ N ₅ O ₃ S	52.79 52.8	3.23 3.2	20.53 20.6	9.38 9.3
g	270	69	C ₁₉ H ₁₄ N ₄ OS	65.90 65.8	4.05 4.0	16.18 16.2	9.25 9.3

* Cl: 10.74
10.8.

Action of Aromatic Amines on 5-Arylazo-4-arylimino-3-phenylhydantoin (VIIa-c)

A mixture of each IIa,b (0.005 mol.) and the appropriate primary aromatic amine (0.0055 mol) was mixed well and then heated in an oil bath at 150—160 °C for 2 hours till the odour of the evolved hydrogen sulphide could no longer be detected. The reaction mixture was left to cool at room temperature and the solid obtained was washed with alcohol and crystallized from acetic acid. The products 5-arylazo-4-arylimino-3-phenylhydantoin derivatives (VIIa-c) are yellow in colour.

VIIa: m. p. 234 °C; yield 85%.

Anal. C₂₁H₁₇N₅O calc'd.: C 70.99; H 4.79; N 19.72%
found: C 71.0; H 4.7; N 19.8 %

VIIb: m. p. 240 °C; yield 81%.

Anal. C₂₂H₁₉N₅O calc'd.: C 71.54; H 5.15; N 18.97%
found: C 71.5; H 5.2; N 19.0 %

VIIc: m. p. 230 °C; yield 75%.

Anal. C₂₃H₂₁N₅O calc'd.: C 72.06; H 5.48; N 18.28%
C 72.0; H 5.5; N 18.3 %

Methylation of 5-(*m*-tolylazo)-3-phenyl-4-methylmercaptopydantoin

To the solution of (0.002 mol) of IIb in 20 ml sodium hydroxide (2%) and ethanol (20 ml) the excess of methyl iodide (2 ml) was added. The red colour of the reaction mixture gradually changed to orange, whereafter precipitation of the product took place. The reaction mixture was left to stand overnight at room temperature. The solid thus obtained was collected by filtration and recrystallized from ethyl alcohol in the form of yellowish orange crystals of 5-(*m*-tolylazo)-3-phenyl-4-methylmercaptopydantoin m. p. 159 °C; yield 72%.

Anal. C₁₇H₁₆N₄OS calc'd.: C 62.96; H 4.94; N 17.28; S 9.88%
found: C 63.0; H 5.0; N 17.31; S 9.80%

Reaction of 5-(*m*-tolylazo)-3-phenyl-4-phenyliminothiohydantoin (VIIb)

A mixture of 0.006 mol of 5-(*m*-tolylazo)-3-phenylmethylmercaptopyridone and 0.0065 mol of aniline was mixed well and then heated in an oil bath at 150–160 °C till the odour of the methane thiol could no longer be detected. The reaction mixture was left to cool, and then washed with alcohol. The residual solid obtained was crystallized from acetic acid m. p. 246 °C. It was proved to be VIIb by melting point and mixed melting point determinations.

Methylation of 3-Phenyl-4-methylmercaptopyridone

To the solution of (0.005 mol) of 3-phenyl-4-thiohydantoin in 11.5 ml sodium hydroxide (2%) and ethanol (15 ml), methyl iodide (0.0055 mol) was added. The reaction mixture was stirred for 15 minutes and left overnight at room temperature. The solid thus obtained was crystallized from ethyl alcohol as colourless crystals of 3-phenyl-4-methylmercaptopyridone m. p. 197 °C.

Anal. $C_{10}H_{10}N_2OS$ calc'd.: C 58.25; H 4.85; N 13.59; S 15.53%
found: C 58.2; H 4.9; N 13.6; S 15.6 %

Preparation of 5-(*m*-tolylazo)-3-phenyl-4-methylmercaptopyridone

To 0.73 ml (0.0068 mol) of *m*-toluidine concentrated hydrochloric acid (6 ml) and water (6 ml) were added. The reaction mixture was cooled to 0 °C and then treated with a cold solution of sodium nitrite (0.6 g) in water (6 ml). The *m*-tolylidiazonium chloride was added gradually to an ice-cold solution of 1.4 g 3-phenyl-4-methylmercaptopyridone dissolved in 50 ml ethanol containing 2.6 g of sodium acetate. After the addition was completed, the reaction mixture was left to stand in a cold chest for 1 hour. The product separated was filtered off, washed with water and crystallized from acetic acid. The obtained compound was proved to be 5-(*m*-tolylazo)-3-phenyl-4-methylmercaptopyridone by melting point and mixed melting point determinations.

Preparation of 5-Arylidene-3-phenyl-4-thiohydantoin (VIIIa-e)

A mixture of 3-phenyl-4-thiohydantoin (0.96 g, 0.005 mol), fused sodium acetate (2 g) and a slight excess (0.0055 mol) of the appropriate aldehyde in 25 ml glacial acetic acid was refluxed for 2 hours. During the heating of the reaction mixture, the solution became dark brownish red. It was left to stand overnight at room temperature and then poured over cold water. The product, separated, was filtered off, and recrystallized from ethyl alcohol. The 5-arylidene-3-phenyl-4-thiohydantoin listed in Table II are orange in colour and they are soluble in hot benzene.

TABLE II
5-Arylidene-3-phenyl-4-thiohydantoin (VIIIa-e)

Compound	M. P. °C	Yield %	Formula	Analysis		Calc'd. Found	
				C/%	H/%	N/%	S/%
VIIIa	223	79	$C_{16}H_{12}N_2OS$	68.57	4.29	10.00	11.43
				68.6	4.3	10.1	11.4
b	241	70	$C_{16}H_{11}N_3O_3S$	59.80	3.38	12.92	9.85
				59.9	3.4	12.8	9.9
c	225	72	$C_{17}H_{14}N_2O_2S$	65.81	4.52	9.03	10.32
				65.9	4.6	9.0	10.4
d	198	80	$C_{16}H_{10}N_2OSCl_2^*$	55.17	2.87	8.05	9.19
				55.2	2.8	8.1	9.0
e	189	82	$C_{18}H_{17}N_3OS$	66.87	5.26	13.00	9.91
				66.9	5.2	12.9	10.0

* Cl: 20.40
20.30.

Action of Alkyl- and Arylmagnesium halides on 5-Arylidene-3-phenyl-4-thiohydantoin Derivatives (VIIIa, d, e)

To a Grignard solution (prepared from 1.0 g magnesium and the appropriate quantity of the alkyl halide or aryl halide in 100 ml of dry ether) 1.0 g of each of VIIIa,d,e dissolved in 50 ml dry benzene was added. The reaction mixture was refluxed over a steam bath for two hours till it acquired a pale yellow colour, left to stand overnight at room temperature, and then decomposed by about 100 ml of saturated aqueous ammonium chloride solution to which 3 ml of concentrated hydrochloric acid was added. The ethereal layer was separated and dried over anhydrous sodium sulphate. The ethereal solution was evaporated over a water-bath, and the residue thus obtained was washed several times with petroleum ether (b. p. 40–60 °C). The obtained substance was crystallized from the benzene-benzine, mixture.

The Grignard products IXa-e listed in Table III are all colourless.

TABLE III

Action of Grignard Reagents on 5-Arylidene-3-phenyl-4-thiohydantoin (VIIIa, d, e)

Compound	M. p. °C	Yield %	Formula	Analysis		Calc'd	S/%
				C/%	H/%	Found N/%	
IXa	110	75	C ₁₈ H ₁₈ N ₂ OS	69.68	5.81	9.03	10.32
				69.7	5.8	9.0	10.4
b	195	70	C ₂₂ H ₁₈ N ₂ OS	73.74	5.03	7.82	8.94
				73.6	5.0	7.9	9.0
c	125	71	C ₂₃ H ₁₈ N ₂ OSCl ₂ ^a	62.59	4.08	6.35	7.26
				62.6	4.0	6.4	7.3
d	158	68	C ₁₈ H ₁₆ N ₂ OSCl ₂ ^b	56.99	4.22	7.39	8.44
				57.0	4.3	7.4	8.5
e	211	60	C ₂₀ H ₂₃ N ₃ OS	67.99	6.52	11.90	9.07
				68.0	6.6	12.0	9.0

^a Cl: 16.10
16.2

^b Cl: 18.73
18.8

Attempted Action of Ethyl Magnesium Iodide on 3-Phenyl-4-thiohydantoin

To an ethereal solution of ethylmagnesium iodide (prepared in a similar manner as above), was added 1 g of 3-phenyl-4-thiohydantoin in 50 ml of dry benzene. The Grignard reaction was worked up as described above and the starting material was recovered unchanged (melting point and mixed melting point determination).

Action of Alkyl- and Arylmagnesium Halides on 5-Benzylidene-3-phenyl-hydantoin

1 g of 5-benzylidene-3-phenylhydantoin (m. p. 262 °C) dissolved in 150 ml of dry benzene was added separately to an ethereal solution of ethylmagnesium iodide and phenylmagnesium bromide (prepared in a similar manner as described above). The Grignard reaction was worked up and the solid, thus obtained, was crystallized from the proper solvent in the form of colourless crystals of (Xa, b).

Xa crystallised from Benzene-benzine mixture: m. p. 175 °C; yield, 70%.

Anal. C₁₈H₁₈N₂O₂ calc'd: C 73.47; H 6.12; N 9.52%
found: C 73.5; H 6.2; N 9.6 %

Xb crystallised from ethyl alcohol: m. p. 169 °C; yield, 68%.

Anal. C₂₂H₁₈N₂O₂ calc'd: C 77.19; H 5.26; N 8.20%
found C 77.2; H 5.3; N 8.3 %

5-Benzhydryl-3-phenyl-4-thiohydantoin (IXa)

2.5 g of Xa were mixed well with 1.5 g of phosphorous pentasulphide then covered with 60 ml of dry dioxane. The reaction mixture was worked up as above. The oily residue, obtained, was solidified by washing with petroleum ether (40—60 °C) and crystallized from benzene-benzine mixture as colourless crystals; m. p. 110 °C. It was proved to be IXa by melting point and mixed melting point determinations.

Cleavage of 5-benzhydryl-3-phenylhydantoin (Xa)

A mixture of 1 g of Xa dissolved in 15 ml of glacial acetic acid and 100 g of chromic acid in 10 ml of glacial acetic acid, was heated on steam-bath for 2 hours. The reaction mixture was kept overnight at room temperature, poured over cold water then extracted with ether. The ethereal layer was evaporated on steam bath. The oily residue was washed with petroleum ether till solidification. The solid, so obtained, was recrystallised from dilute acetic acid as colourless crystals, m. p. 205 °C. It was proved to be phenyl parabanic acid by melting point and mixed melting point determinations.¹⁵

The residual organic solvents from the above reaction was evaporated on steam bath till dryness. The oily substance, was dissolved in 5 ml ethanol followed by the addition of 1 g of 2:4-dinitrophenyl hydrazine dissolved in alcohol. The reaction mixture was left till precipitation of red crystals, m. p. 187—9 °C. It was proved to be 2,4-dinitrophenyl hydrazone derivative of ethyl phenyl ketone by melting point and mixed melting point determination.¹⁶

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SAŽETAK

Reakcije s derivatima 5-arilazo- i 5-ariliden-4-hidantoina

A. F. A. Shalaby, M. A. Abdel Aziz i M. A. Abd Allah

Reakcijom primarnih aromatskih amina s 5-aril-3-fenil-4-tiohidantoinima (IIa-g), pripremljeni su odgovarajući 5-arilazo-4-arilimino-3-fenil hidantoini (VIIa-c). 3-Fenil-4-tiohidantoin reagira s aromatskim aldehidima, u prisutnosti ledene octene kiseline i natrijevog acetata, dajući 5-ariliden-3-fenil-4-tiohidantoina (VIIIa-e). Adicijom alkil i/ili arilmagnezijevih halida na egzociklički dvostruki vez obojenih arilidenskih derivata (VIIIa, d, e), nastaju produkti (IXa-e). Oksidacijom grignardovog spoja (Xa) smjesom kromne i ledene octene kiseline, dobivena je fenilparabanska kiselina i fenilmetilketon.

CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE,
CAIRO UNIVERSITY, GIZA, EGYPT

Prispjelo 5. travnja 1979.