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BEHAVIOR OF THE HETERO-RING IN γ-PHENYL-$\Delta^{\beta,\gamma}$-BUTENOLIDE DERIVATIVES TOWARD HYDRAZINES. ACID REARRANGEMENT OF 4-PHENYLAZO-2-PHENYLOXAZOLIN-5-ONE

AHMED MUSTAFA, SAMIR A. KHATTAB, AND WAFIA ASKER
Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt, U.A.R.

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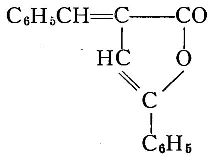
ABSTRACT

The substituted pyridazinones 3-phenyl- and 1,3-diphenyl-5-benzylidene-1,4,5,6-tetrahydropyridazinone-6 have been prepared from α-phenacylcinnamic acid hydrazide and α-phenacylcinnamic acid phenylhydrazone, respectively. The dipyridazinone 5,5-di(3-phenyl-1,4,5,6-tetrahydro)pyridazinone-6 was prepared from the dilactone IV, isolated as a side product in the synthesis of lactone VI.

Rearrangement of 4-phenylazo-2-phenyloxazolin-5-one now has been found to proceed also in the presence of acidic reagents.

α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide* (I) has been reported to undergo ring opening upon treatment with aqueous base, with methanol under both acidic and basic conditions (1, 2) and with benzylamine (1) to form α-phenacylcinnamic acid (II*a*), its methyl ester (II*b*), and its benzylamide derivative (II*e*) respectively.

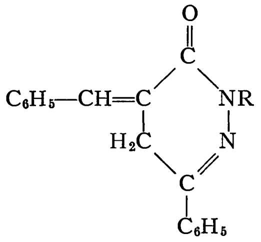


I

$C_6H_5CH{=}C(CH_2{-}COC_6H_5)COR$

II*a*, R = OH
b, R = OCH_3
c, R = $NHNH_2$
d, R = $NHNHC_6H_5$
e, R = $NHCH_2C_6H_5$

This investigation was undertaken with a view to study the behavior of the hetero-ring in compound I toward the action of hydrazines. Treatment of compound I with hydrazine hydrate effected ring opening with the formation of α-phenacylcinnamic acid hydrazide (II*c*). The latter compound underwent ring closure upon treatment with hydrochloric acid – acetic acid mixture or with aqueous sodium hydroxide solution with the formation of 3-phenyl-5-benzylidene-1,4,5,6-tetrahydropyridazinone-6 (III*a*) (or its tautomer).



III*a*, R = H
b, R = C_6H_5

The proposed structure for the hydrazide II*c* finds support from the fact that this compound was readily obtained via treatment of methyl α-phenacylcinnamate (II*b*) with

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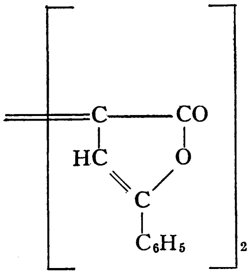
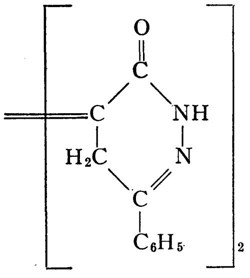
**This nomenclature is after that used by Filler (1).*

hydrazine hydrate. Compound III*a* was also found to be identical with an authentic specimen prepared after Thiele (2).

When the dilactone IV was treated with hydrazine hydrate, 5,5′-di(3-phenyl-1,4,5,6-tetrahydro)pyridazinone-6 (V) (or its possible tautomer) was isolated, but not the corresponding acyclic hydrazide.



IV

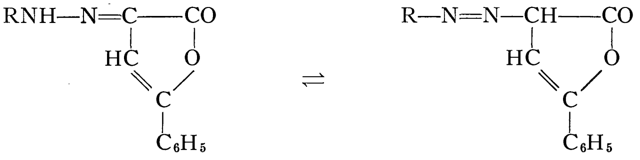


V

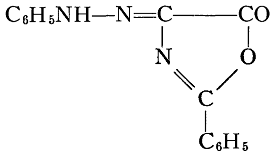
α-Phenacylcinnamic acid (II*a*), upon treatment with phenylhydrazine, gave the corresponding phenylhydrazone derivative. When the latter compound was treated with hot sodium hydroxide solution, it underwent ring closure with the formation of 1,3-diphenyl-5-benzylidene-1,4,5,6-tetrahydropyridazinone-6 (III*b*). The assigned structure for the latter compound finds support from its identity with a sample obtained via the condensation of 1,3-diphenyl-1,4,5,6-tetrahydropyridazinone-6 with benzaldehyde (3).

Phenylhydrazine was found to react with compound I, not to form the phenylhydrazone derivative of α-phenacylcinnamic acid but to give a colorless product believed to be α-phenacylcinnamic acid phenylhydrazide (II*d*).

Dieckmann described the preparation of α-phenylazo-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VI*a*) by coupling of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide with benzenediazonium chloride (4). We have succeeded in preparing a number of α-arylazo-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides, VI*a–d*, after the procedure described by Sawdey (5) for the preparation of 4-phenylazo-2-phenyloxazolin-5-one (VII) using β-benzoylpropionic acid for hippuric acid. Work-up of the filtrate of the reaction mixture, after separation of the reaction products VI*a–d*, gave dark red crystals identical with the dilactone IV (6, 7).



VI*a*, R = C_6H_5
b, R = C_6H_4—CH_3 (*p*)
c, R = C_6H_4—Cl (*m*)
d, R = C_6H_4—Cl (*p*)



VII

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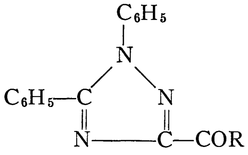
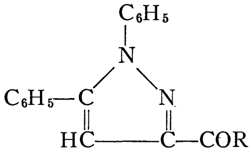
While the rearrangement of 4-phenyl-azo-2-phenyloxazolin-5-one (VII) and its carbon analogue α-phenylazo-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VI*a*) was in progress in this laboratory (8), Browne and Polya (9, 10) reported the rearrangement of compound VII in the presence of basic reagents, a fact which prompts us to record our findings. Results in our hands confirm the findings of the latter authors, but we would like to report that the rearrangement of compound VII to 1,5-diphenyl-1,2,4-triazole-3-carboxylic acid hydrazide (VIII*c*) with hydrazine hydrate can be brought about in the absence of solvent. Hydrolysis of the hydrazide VIII*c* to the corresponding 1,5-diphenyl-1,2,4-triazole-3-carboxylic acid (VIII*a*) is readily effected by the action of hydrochloric acid – acetic acid mixture.



VIII*a*, R = OH
b, R = OCH_3
c, R = $NHNH_2$



IX*a*, R = OH
b, R = OC_2H_5
c, R = $NHNH_2$

We would like also to record that, though the latter authors reported that the rearrangement of compound VII did not occur in solutions acid to litmus, in our hands treatment of this compound with hydrochloric acid – acetic acid mixture yielded the triazole acid VIII*a* in a yield similar to that obtained by alkali rearrangement (5).

The carbon analogue VI*a* underwent rearrangement by action of alcoholic alkali or hydrochloric acid – acetic acid mixture to give the corresponding 1,5-diphenylpyrazole-3-carboxylic acid (IX*a*) (4). The ethyl ester IX*b*, now obtained from the corresponding acid IX*a*, reacts with hydrazine hydrate to give 1,5-diphenylpyrazole-3-carboxylic acid hydrazide (IX*c*).

EXPERIMENTAL

All melting points are uncorrected.

Action of Hydrazine Hydrate

(a) On α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (I)

Hydrazine hydrate (4 ml, 80%) was added to compound I (0.5 g) and the reaction mixture was allowed to stand at room temperature for half an hour with occasional shaking. The yellow color of compound I was completely discharged with the formation of a colorless deposit of α-phenacylcinnamic acid hydrazine (II*c*). It was collected, washed thoroughly with water, and upon crystallization from ethanol, gave colorless crystals, m.p. 185° (decomp.). Yield, ca. 53%.

Anal. Calc. for $C_{17}H_{16}N_2O_2$: C, 72.85; H, 5.71; N, 10.00. Found: C, 73.07; H, 5.93; N, 9.95.

It gave a red color with concentrated sulphuric acid and was found insoluble in cold aqueous sodium carbonate solution (1%). The infrared spectrum* showed well-defined absorption bands at 1650 cm^{-1} characteristic of the —CONH— group (11) and at 1700 cm^{-1} characteristic of the $—COC_6H_5$ group.

The hydrazide II*c* could also be obtained from methyl α-phenacylcinnamate (II*b*) and hydrazine hydrate in 80% yield when the reaction mixture was allowed to stand for 48 hours under the experimental conditions described above.

(b) On Dilactone IV

The reaction was carried out as for compound I and the mixture was left for 2 weeks. The product, 5,5′-di(3-phenyl-1,4,5,6-tetrahydro)pyridazinone-6 (V), was crystallized from acetic acid as colorless crystals (65% yield), m.p. >350°.

Anal. Calc. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.65; N, 16.27. Found: C, 69.87; H, 4.85; N, 16.19.

**The infrared spectra were produced on a Perkin–Elmer Infracord model 137B and the samples were examined in Nujol solution.*

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Ring Closure of Hydrazide IIc

Method (a)

A mixture of glacial acetic acid (7 ml), hydrochloric acid (3.5 ml), and hydrazide II*c* (0.5 g) was refluxed for 1 hour. The cooled reaction mixture was poured into ice-cold water, and the precipitate so obtained was collected and washed thoroughly with water. It gave colorless crystals of 3-phenyl-5-benzylidene-1,4,5,6-tetrahydropyridazinone-6 (III*a*) from ethanol, m.p. 177°. Yield, ca. 43%.

Anal. Calc. for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.68. Found: C, 77.56; H, 5.46; N, 10.87.

Compound III*a* was proved to be identical with an authentic specimen prepared after Thiele (2) (mixed m.p. determination and identical infrared spectrum).

Method (b)

Aqueous sodium hydroxide solution (10 ml, 4%) was added to hydrazide II*c* (0.3 g) and the reaction mixture was refluxed for half an hour. It was then allowed to cool, diluted with water, and acidified with hydrochloric acid. The precipitated solid was collected, washed with water, and crystallized from ethanol to give colorless crystals of compound III*a*. Yield, ca. 35%.

Action of Phenylhydrazine

(a) On α-Phenacylcinnamic Acid (IIa)

Freshly distilled phenylhydrazine (3.0 g) was added to a suspension of the acid II*a* (3.0 g) in absolute ethanol (30 ml). The reaction mixture was refluxed for 5 hours. On evaporation of the solvent, an oily residue was obtained which after trituration with hot petroleum ether (b.p. 70–80°) was solidified to a pale yellow solid. Upon two crystallizations from the same solvent, it gave almost colorless crystals, m.p. 101° (slight decomp.); yield, 50%; identified as the phenylhydrazone derivative of the acid II*a*.

Anal. Calc. for $C_{23}H_{20}N_2O_2$: N, 7.86. Found: N, 7.66.

When a mixture of the above phenylhydrazone derivative (0.5 g), sodium hydroxide solution (20 ml, 4%), and ethanol (10 ml) was refluxed for 1 hour, it gave upon cooling a colorless deposit of 1,3-diphenyl-5-benzylidene-1,4,5,6-tetrahydropyridazinone-6 (III*b*). The latter was collected, washed with water, and crystallized from ethanol as colorless crystals, m.p. 124°. Yield, ca. 53%.

Anal. Calc. for $C_{23}H_{18}N_2O$: C, 81.65; H, 5.32; N, 8.28. Found: C, 81.61; H, 5.38; N, 8.28.

The product III*b* was found to be identical (m.p. and mixed m.p. determination, infrared spectral comparison, and color with concentrated sulphuric acid) with a sample obtained via the condensation of 1,3-diphenyl-1,4,5,6-tetrahydropyridazinone-6 with benzaldehyde (3).

(b) On α-Benzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (I)

Phenylhydrazine (0.4 g) was added to a suspension of compound I (1.0 g) in absolute ethanol (30 ml). The reaction mixture was refluxed for 5 hours and then the solvent was evaporated. The oily product so obtained was solidified on trituration with cold ether or petroleum ether and was crystallized from ethanol to give colorless crystals of α-phenacylcinnamic acid phenylhydrazide (II*d*), m.p. 207° (decomp.). Yield, ca. 28%.

Anal. Calc. for $C_{23}H_{20}N_2O_2$: C, 77.52; H, 5.61; N, 7.86. Found: C, 77.41; H, 5.58; N, 8.01.

It gave a yellowish red color with concentrated sulphuric acid and was found to be insoluble in cold sodium carbonate solution (1%). The infrared spectrum showed well-defined absorption bands at 1650 cm^{-1} characteristic of the —CONH— group (11) and at 1700 cm^{-1} characteristic of the $—COC_6H_5$ group.

Preparation of α-Arylazo-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides (VIa–d)

The following exemplifies the procedure: To a solution of freshly distilled aniline (3.7 g) in glacial acetic acid (15 ml) was added hydrochloric acid (8 ml), then while the mixture was being cooled in ice and stirred, isoamyl nitrite (8 g) was added dropwise. To the diazonium mixture was added freshly fused sodium acetate (6.0 g). β-Benzoylpropionic acid (10.0 g) was added to acetic anhydride (40 ml) and the mixture was refluxed for 3 hours then allowed to cool to room temperature. This solution was added dropwise, with stirring and cooling in ice, to the diazonium mixture. The reaction mixture was allowed to stand overnight and the precipitated solid was collected, washed with water several times, and crystallized from a large volume of acetic acid.

The arylazo derivatives VI*a–d* (listed in Table I) ranged in color from brownish yellow to deep brown and were found to be sparingly soluble in common organic solvents. They showed an absorption maximum at 350 mμ, which was attributed to the arylhydrazone group (12).

α-Phenylazo-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VI*a*) was proved to be identical with an authentic specimen prepared after Dieckmann (4) (mixed m.p. determination and infrared spectral comparisons).

The mother liquors, after filtration of the products VI*a–d*, gave upon concentration and trituration with ether a dark red solid which was crystallized from xylene or acetic acid as dark red crystals of the dilactone IV in a yield which varied from 5–10%.

Anal. Calc. for $C_{20}H_{12}O_4$: C, 75.94; H, 3.79. Found: C, 75.84; H, 4.02.

The dilactone IV was identical with an authentic specimen prepared after Rogert and Ritter (6).

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TABLE I

The arylazo derivatives (VI*a*–*d*)

Arylazo derivative	M.p. (°C)	Yield (%)	Color with conc. H_2SO_4	Formula	Carbon (%)		Hydrogen (%)		Nitrogen (%)		Chlorine (%)	
					Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
VI*a*	227 (decomp.)	45	Violet	$C_{16}H_{12}N_2O_2$	72.73	72.45	4.54	4.63	10.61	10.53	—	—
VI*b*	222 (decomp.)	40	Dark brown	$C_{17}H_{14}N_2O_2$	73.38	73.88	5.03	5.11	10.07	10.20	—	—
VI*c*	238 (decomp.)	37	Deep violet	$C_{16}H_{11}ClN_2O_2$	64.32	64.37	3.68	3.84	9.38	9.08	11.89	12.12
VI*d*	252 (decomp.)	41	Deep violet	$C_{16}H_{11}ClN_2O_2$	64.32	64.57	3.68	3.77	9.38	9.68	11.89	11.57

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Formation of 1,5-Diphenyl-,1,2,4-triazole-3-carboxylic Acid Hydrazide (VIIIc)

(a) From 4-Phenylazo-2-phenyloxazolin-5-one (VII)

Hydrazine hydrate (5 ml) was added to a suspension of compound VII (1.0 g) in ethanol (30 ml). On shaking the reaction mixture for 15 minutes at room temperature, the orange color of compound VII disappeared with the formation of a colorless deposit. It was allowed to stand overnight, poured into water, and the precipitated solid was collected, washed with water, and crystallized from ethanol or chlorobenzene as colorless crystals of the hydrazide VIII*c*, m.p. 185°. Yield, ca. 42%.

Anal. Calc. for $C_{15}H_{13}N_5O$: C, 64.51; H, 4.65; N, 25.08. Found: C, 64.33; H, 4.84; N, 25.21.

The hydrazide VIII*c* could also be obtained in an almost quantitative yield when a suspension of compound VII (0.6 g) in hydrazine hydrate (10 ml) was allowed to stand for 6 weeks at room temperature.

(b) From 1,5-Diphenyl-3-carbomethoxy-1,2,4-triazole (VIIIb)

Compound VIII*c* was obtained either by allowing a suspension of the ester VIII*b* (0.3 g) in hydrazine hydrate (3 ml) to stand at room temperature for 4 weeks (yield was ca. 60%) or by heating the same suspension on the direct flame until the ester dissolved in the medium and then continuing the heating on a boiling-water bath for 15 hours. Yield, ca. 33%.

Hydrolysis of 1,5-Diphenyl-1,2,4-triazole-3-carboxylic Acid Hydrazide (VIIIc)

The hydrazide VIII*c* (0.5 g) was treated with a mixture of glacial acetic acid (15 ml) and hydrochloric acid (20 ml). The reaction mixture was refluxed for 3 hours, cooled, and poured into water. The solid so obtained was collected, washed with water, and crystallized from benzene as colorless crystals of 1,5-diphenyl-1,2,4-triazole-3-carboxylic acid (VIII*a*), m.p. 181° (decomp.), not depressed when admixed with an authentic specimen prepared after Sawdey (5). Yield, ca. 63%.

Action of Hydrochloric Acid – Acetic Acid Mixture on 4-Phenylazo-2-phenyloxazolin-5-one (VII)

Compound VII (2.0 g) was treated with a mixture of glacial acetic acid (40 ml) and hydrochloric acid (60 ml) and the reaction mixture was refluxed for 5 hours. Working up of the reaction product as above gave the acid VIII*a*. Yield, ca. 80%.

Preparation of 1,5-Diphenyl-3-carbethoxypyrazole (IXb)

To 1,5-diphenylpyrazole-3-carboxylic acid (IX*a*) (1.0 g) was added absolute ethanol (25 ml) and concentrated sulphuric acid (0.5 ml) and the reaction mixture was refluxed on a boiling-water bath for 5 hours. It was cooled, poured into ice-cold sodium carbonate solution (100 ml, 0.5%) and the solid obtained was collected, washed with water, and crystallized from dilute ethanol (1:1) as colorless crystals of the ethyl ester IX*b*, m.p. 90° not depressed when admixed with an authentic specimen (13, 14). Yield, ca. 77%.

Formation of 1,5-Diphenylpyrazole-3-carboxylic Acid Hydrazide (IXc) from the Ethyl Ester IXb

Method (a)

The ester IX*b* (1.0 g) was heated with hydrazine hydrate (5.5 ml) on a boiling-water bath for half an hour, then absolute ethanol (20 ml) was added to the reaction mixture, which was then refluxed for 3 hours. It was allowed to cool and then poured into water. The hydrazide IX*c* was collected, washed with water, and upon crystallization from ethanol, colorless crystals were obtained, m.p. 174°. Yield, ca. 63%.

Anal. Calc. for $C_{16}H_{14}N_4O$: C, 69.06; H, 5.03; N, 20.14. Found: C, 69.16; H, 5.27; N, 20.25.

Method (b)

The same hydrazide could also be obtained in a similar yield as above when a mixture of the ester IX*b* (1.0 g) and hydrazine hydrate (6 ml) was allowed to stand at room temperature for 1 week.

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