

Reaction of levulinic acid and its ethyl ester with hydrazine derivatives

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ABSTRACT

Reaction of levulinic acid and its ethyl ester with benzoyl-, α -naphthoyl-, phenylacetyl- and α -naphthylacetyl-hydrazines and ethyl hydrazinecarboxylate gave the corresponding hydrazones (III) which upon treatment with concentrated sulphuric acid afforded 6-keto-3-methyl-1,4,5,6-tetrahydropyridazine (V) and the corresponding acid (VI). Heating of these hydrazones at 160–170°C gave the corresponding diacyl- or diaroylhydrazines (IV).

The structure of the products was established by chemical and spectroscopic evidence.

INTRODUCTION

The reaction of levulinic acid with hydroxylamine, hydrazine hydrate, and phenylhydrazine has been reported to give the corresponding oxime and hydrazones (Kitano *et al.* 1975).

The present work was intended to study the structure and the properties of the products obtained from the reaction of levulinic acid and its ethyl ester with aroyl- and acylhydrazines, and ethyl hydrazinecarboxylate.

RESULTS AND DISCUSSION

When levulinic acid and ethyl levulinate were refluxed with an alcoholic solution of benzoyl-(IIa), phenylacetyl-(IIb), α -naphthoyl-(IIc), and α -naphthylacetyl-(IId) hydrazines and ethyl hydrazinecarboxylate (IIe), they gave the corresponding hydrazone derivatives (IIIa–j) (cf. Scheme 1). The reactions seem to be similar to the reaction of hydrazine derivatives with ethyl acetoacetate (Evans *et al.* 1965).

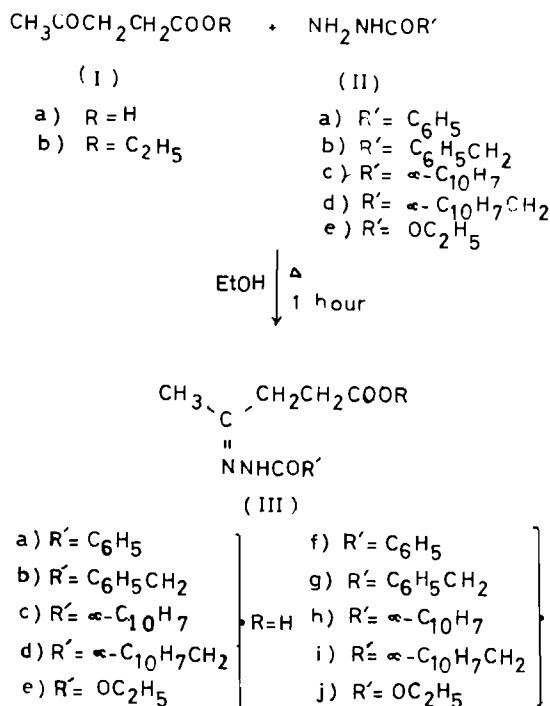
The structure of the above products was established spectroscopically and chemically.

(i) Spectroscopic evidence for the structure of hydrazones (IIIa–j):

The structure of the hydrazones (IIIa–j) was substantiated by their i.r. and n.m.r. spectra (cf. Table 1).

(ii) Chemical evidence:

The following chemical reactions of compounds (IIIa–j) give further evidence for the assigned structure.



Scheme 1

(a) They are converted to a mixture of the corresponding 6-keto-3-methyl-1,4,5,6-tetrahydropyridazine (V) and acids (VI) when heated with 3% methanolic potassium hydroxide on a boiling water-bath or with concentrated sulphuric acid at 160–170°C. Authentic sample of (V) was obtained by heating levulinic acid or its ethyl ester with hydrazine hydrate at 120–125°C for 6 hr (cf. Scheme 2).

(b) Heating of these compounds (IIIa–d and IIIf–i) at 160–170°C gave the corresponding 1,2-diaroyl-(IVa,c) and 1,2-diacyl-(IVb,d)-hydrazines in addition to a polymeric product, which is still under investigation. The structure of (IVa–d) was established by their identity with authentic samples prepared by heating aroyl-(IIa,c) and acyl-(IIb,d)-hydrazines with the corresponding aroyl and acyl chlorides in pyridine (Baddar *et al.* 1978).

The dissociation constants of the hydrazones of levulinic acid (IIIa–c) were determined using a potentiometric method (Isaacs 1970, pp. 8–14) by evaluating the pH of a dilute solution of the acid at half neutralisation with sodium hydroxide. Results are reported in Table 2.

Fig. 1 shows the potentiometer titration curve between the pH and the amount of the sodium hydroxide solution added for compound (IIIc). These results indicated that the pK_a values of the different acids (IIIa–e) are higher than that of levulinic acid (pK_a 4.60, reported 4.50, Kitano *et al.* 1975). The difference may be attributed to the effect of the weak hydrogen bonding between the carbonyl group of the acid and the NH group. The acids (IIIa) and (IIIc) have higher pK_a values (5.10 and 5.15 respectively) than

Table 1. Infrared and nuclear magnetic resonance spectral data of the hydrazone derivatives (IIIa-j)

Compound	Infrared spectra (Nujol)		N.m.r. spectra (CDCl ₃)	
	cm ⁻¹	ν	δ	Assignments (no. of protons)
IIIa	3200 (br.)	NH	9.28 (br.)	(1) NH
	3100-2200 (br.)	COOH	8.05-7.05 (m)	(5) ArH
	1710 (s)	C=O	2.65 (m)	(4) CH ₂ CH ₂
	1640 (s)	CO of amide	1.97 (s)	(3) CH ₃
IIIb	3200 (br.)	NH	9.87 (br.)	(1) NH
	2900-2000 (br.)	COOH	7.47-7.10 (m)	(5) ArH
	1700 (s)	C=O	3.93 (s)	(2) CH ₂ Ar
	1640 (s)	C=O of amide	2.58 (m)	(4) CH ₂ CH ₂
IIIc	3400-2400 (br.)	NH	10.5 (br.)	(1) NH
	3240 (br.)	COOH	8.47-7.1 (m)	(7) ArH
	1710 (s)	C=O	2.58 (m)	(4) CH ₂ CH ₂
	1660 (s)	C=O of amide	2.0 (s)	(3) CH ₃
III d	3400-2400 (br.)	NH	9.37 (br.)	(1) NH
	3260 (br.)	COOH	8.3-7.30 (m)	(7) ArH
	1710 (s)	C=O	4.40 (s)	(2) CH ₂ Ar
	1660 (s)	C=O of amide	2.63 (m)	(4) CH ₂ CH ₂
IIIe	3200 (br.)	NH	1.88 (s)	(3) CH ₃
	3400-2400 (br.)	COOH	8.2 (br.)	(1) NH
	1740 (s)	CO of ester	4.28 (q)(J = 7Hz)	(2) CH ₂ CH ₃
	1710 (s)	CO of acid	2.63 (m)	(4) CH ₂ CH ₂
III f	1640 (s)	CO of amide	1.92 (s)	(3) CH ₃
	3260 (br.)	NH	1.32 (t)(J = 7Hz)	(3) CH ₂ CH ₃
	1730 (s)	CO of ester	8.95 (br.)	(1) NH
	1680 (s)	C=O of amide	8.25-7.25 (m)	(5) ArH
III g	3260 (br.)	NH	4.18 (q)(J = 7Hz)	(2) CH ₂ CH ₃
	1730 (s)	CO of ester	2.65 (m)	(4) CH ₂ CH ₂
	1680 (s)	C=O of amide	1.98 (s)	(3) CH ₃
			1.25 (t)(J = 7Hz)	(3) CH ₂ CH ₃
III h	3260 (br.)	NH	9.2 (br.)	(1) NH
	1730 (s)	CO of ester	7.33 (s)	(5) ArH
	1680 (s)	C=O of amide	4.14 (q)(J = 7Hz)	(2) CH ₂ CH ₃
			3.95 (s)	(2) CH ₂ Ar
III i	3260 (br.)	NH	2.60 (m)	(4) CH ₂ CH ₂
	1735 (s)	C=O of ester	1.83 (s)	(3) CH ₃
	1670 (s)	C=O of amide	1.23 (t)(J = 7Hz)	(3) CH ₂ CH ₃
			9.23 (br.)	(1) NH
III j	3260 (br.)	NH	8.33-6.80 (m)	(7) ArH
	1730 (s)	C=O of ester	4.22 (q)(J = 7Hz)	(2) CH ₂ CH ₃
	1660 (s)	C=O of amide	2.60 (m)	(4) CH ₂ CH ₂
			1.67 (s)	(3) CH ₃
III k	3200 (br.)	NH	1.17 (t)(J = 7Hz)	(3) CH ₂ CH ₃
	1735 (s)	C=O of ester	8.68 (br.)	(1) NH
	1670 (s)	C=O of amide	8.25-7.25 (m)	(5) ArH
			4.12 (q)(J = 7Hz)	(2) CH ₂ CH ₃
III l	3220 (br.)	NH	2.63 (m)	(4) CH ₂ CH ₂
	1740 (s), 1730 (s)	C=O of ester	1.80 (s)	(3) CH ₃
	1660 (s)	C=O of amide	1.18 (t)(J = 7Hz)	(3) CH ₂ CH ₃
			7.93 (br.)	(1) NH
III m	3220 (br.)	NH	4.28 (q)(J = 7Hz)	(4) CH ₂ CH ₃
	1740 (s), 1730 (s)	C=O of ester	2.62 (s)	(4) CH ₂ CH ₂
	1660 (s)	C=O of amide	1.87 (s)	(3) CH ₃
			1.28 (t)	(3) CH ₂ CH ₃
III n	1660 (s)	C=O of amide	1.32 (t)(J = 7Hz)	(3) CH ₂ CH ₃
			1.32 (t)(J = 7Hz)	(3) CH ₂ CH ₃

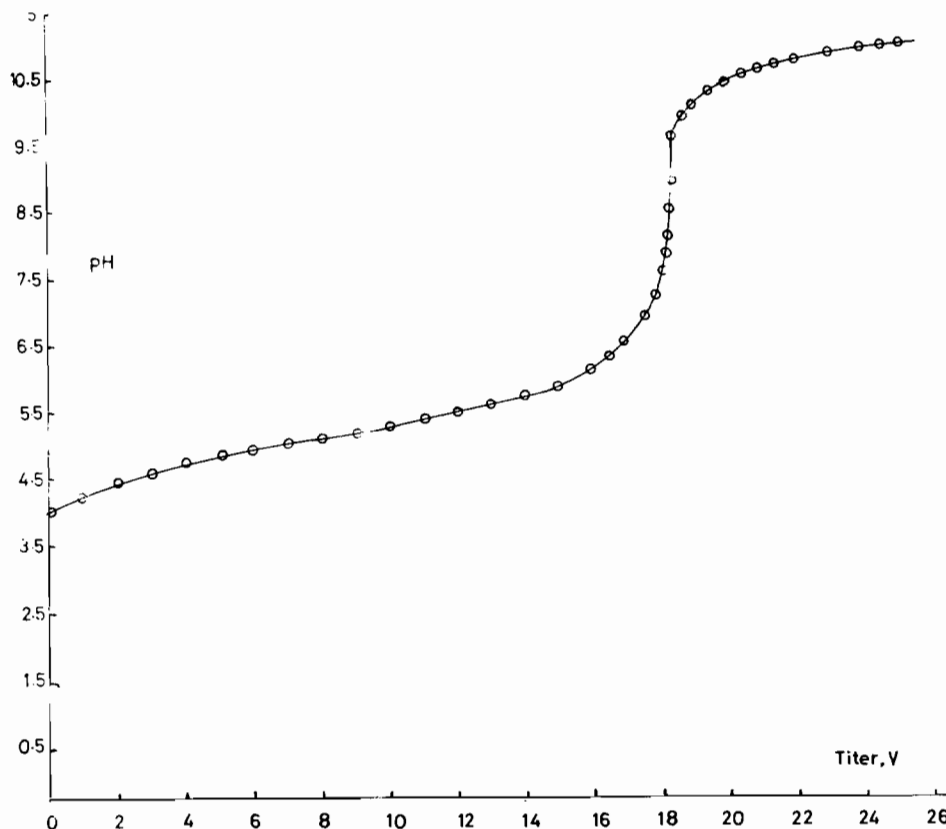
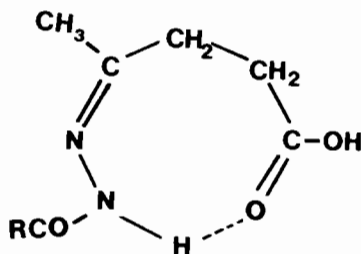


Fig. 1. Potentiometric titration of the acid (IIIc).

those of the other acids (IIIb, d, e) (pK_a values in the range 4.80–4.96). This result may be due to the fact that the NH group in the acids (IIIa and IIIc) is attached directly to



the highly conjugated COAr group, whereas in the other acids (III_b and III_d), the carbonyl group is separated from the aryl nucleus by a CH₂ group (Albert & Serjeant 1971, p. 3).

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer 577 Grating infrared spectrometer (potassium bromide). N.m.r. spectra were measured on

a Jeol JNM-PMX 60 spectrophotometer using TMS as internal standard. The purity of the analytical samples was checked by TLC (silica gel). Microanalyses were determined by Alfred Bernhardt, West Germany. All evaporations were performed on a rotary evaporator *in vacuo*.

Reaction of levulinic acid and its ethyl ester with acyl- or aroylhydrazines and ethyl hydrazinecarboxylate

A mixture of levulinic acid or its ethyl ester (0.01 mole) and acyl- or aroylhydrazine or ethyl hydrazinecarboxylate (0.01 mole) was refluxed in ethanol (50 ml) for 1 hr. The reaction mixture was concentrated, and the product, precipitated on cooling, was crystallised from benzene-cyclohexane to give the corresponding hydrazones (IIIa-j). The results are reported in Table 3.

Table 3. Physical data of hydrazones (IIIa-j)

Compound	M.p. °C	Yield (%)	Found (%)			M.F.	Required (%)		
			C	H	N		C	H	N
IIIa	135-136	98	61.41	6.11	11.82	C ₁₂ H ₁₄ N ₂ O ₃	61.53	6.02	11.96
IIIb	122-123	99	62.55	6.41	11.43	C ₁₃ H ₁₆ N ₂ O ₃	62.89	6.50	11.28
IIIc	175-176	95	67.61	5.52	9.78	C ₁₆ H ₁₆ N ₂ O ₃	67.59	5.67	9.85
IIId	183-184	96	68.53	6.15	9.44	C ₁₇ H ₁₈ N ₂ O ₃	68.44	6.08	9.39
IIIe	106-107	98	47.67	7.02	13.63	C ₈ H ₁₄ N ₂ O ₃	47.52	6.98	13.85
IIIf	113-114	97	64.07	6.79	10.89	C ₁₂ H ₁₄ N ₂ O ₃	64.11	6.92	10.68
IIIg	112-113	95	65.42	7.52	10.43	C ₁₅ H ₂₀ N ₂ O ₃	65.20	7.30	10.14
IIIh	120-121	94	69.51	6.52	9.14	C ₁₈ H ₂₀ N ₂ O ₃	69.21	6.45	8.97
IIIi	83-84	92	70.15	6.55	8.82	C ₁₉ H ₂₂ N ₂ O ₃	69.92	6.79	8.58
IIIj	67-68	88	52.52	7.96	12.44	C ₁₀ H ₁₈ N ₂ O ₄	52.16	7.88	12.17

Reaction of levulinic acid and its ethyl ester with hydrazine hydrate

A mixture of levulinic acid or ethyl levulinate (0.01 mole) and hydrazine hydrate (99% w/w; 3 ml) was heated at 120-125°C on an oil-bath for 6 hr. The sublimated colourless needles were proved to be 6-keto-3-methyl-1,4,5,6-tetrahydropyridazine, m.p. and mixed m.p. 104-105°C (purified by sublimation at normal pressure, Kitano *et al.* 1975).

The i.r. spectrum of the pyridazine derivative (V) shows a broad band at 3,330-3,320 cm⁻¹ (νNH) and a strong band at 1,660 cm⁻¹ (νC=O of amide). Its n.m.r. spectrum shows a broad signal at δ8.5 (NH), exchanged with deuterium oxide. The methylene protons gave a multiplet signal at δ2.56 (4H), whereas the methyl protons gave a sharp signal at δ2.10 (3H).

1,2-Diacyl- and diaroylhydrazines (Baddar et al. 1978)

The acyl- or aroylchloride (0.01 mole) was added dropwise to a stirred solution of acyl- or aroylhydrazine (0.01 mole) (prepared by stirring the corresponding ester with hydrazine hydrate on a boiling water-bath for 1 hr) in pyridine (50 ml) at room temperature, and kept for 1 hr.

The reaction mixture was diluted with water and filtered off. The colourless solids were crystallised from pyridine–water to give the corresponding 1,2-diacyl- or diaroyl-hydrazines (IV) as colourless leaflets.

1,2-Dibenzoyl hydrazine (IVa). This compound had m.p. 234–235°, yield = 98%.

1,2-Di(phenylacetyl) hydrazine (IVb). This compound had m.p. 243–244°, yield = 92%.

1,2-Di(α -naphthoyl) hydrazine (IVc). This compound had m.p. 265–266°, yield = 88%.

1,2-Di(α -naphthylacetyl) hydrazine (IVd). This compound had m.p. 292–293°, yield = 72%.

Action of heat on the hydrazones (IIIa–j)

The hydrazone (III) (1.0 g) was heated on an oil-bath (160–170°) for 15 min. The reaction mixture was treated with chloroform and the precipitated solid was filtered off. Crystallisation of the solid product from pyridine–water gave the corresponding diacyl- or diaroylhydrazine (IV), identified by m.p. and mixed m.p., and i.r. spectra in 40–48% yield.

Evaporation of the chloroform afforded a polymer product which is still under investigation.

Action of concentrated sulphuric acid on the hydrazone derivative (IIIa–j)

A mixture of the hydrazone (III) (1.0 g) and concentrated sulphuric acid (5 ml) was heated on an oil-bath at 150–160° for 15 min. The reaction mixture was poured into cold water (50 ml) and the precipitated acid was filtered off. Crystallisation was made from benzene–light petroleum (60–80°) and the colourless crystals were proved to be the corresponding acid (VI). The aqueous acidic solution was neutralised with sodium carbonate and concentrated on a rotary evaporator *in vacuo*. The residual oily material was heated on an oil-bath at 120–125° for 2 hr. The colourless sublimate was collected and proved to be 6-keto-3-methyl-1,4,5,6-tetrahydropyridazine (m.p. and mixed m.p. 104–105°); yield = 35%.

Action of 3% methanolic potassium hydroxide on the hydrazones (III–h)

A mixture of the hydrazone (III) (0.05 mole) and 3% methanolic potassium hydroxide (25 ml) was heated on a boiling water-bath for 30 min. The solvent was evaporated and the residual solid heated on an oil-bath at 120–125° for 1 hr. The colourless sublimate was collected and proved to be 6-keto-3-methyl-1,4,5,6-tetrahydropyridazine (m.p. and mixed m.p. 104–105°). The residual mixture was dissolved in water (25 ml), then acidified with dilute sulphuric acid and the precipitated solid was filtered off. The colourless solid was crystallised from benzene–light petroleum (60–80°) to give the corresponding acid (VI) (m.p. and mixed m.p.).

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(Received 13 June 1978)

تفاعل حمض الليثولينييك وأستره الايثلي مع مشتقات الهيدرازين

فاروق الحجار و علي عناني و يوسف السلطان
قسم البترول والبتروكياويات ، معهد الكويت للأبحاث العلمية

خلاصة

يتفاعل حمض الليثولينييك وأستره الايثلي مع مشتقات البنزويل والفا - نفثويل وفينيل - اسيتيل - والفا - نفثيل - استيل الهيدرازين والاستر الايثلي لكاربوكسيلات الهيدرازين ليعطي الهيدرازونات المقابلة (III) والتي تتحول بدورها إلى ٦ - كيتو - ٣ - ميثل - ١ ، ٤ ، ٥ ، ٦ ، - رابع هيدروبيريدازين (V) والحمض المقابل عند معالجتها بحمض الكبريتيك المركز. وبتسخين هذه الهيدرازونات عند درجة حرارة ١٦٠-١٧٠° تعطي ما يقابلها من ثنائي أسيل أو ثنائي أرويل الهيدرازين (IV) . وقد تم تحديد التركيب الكيميائي لهذه المركبات بالطرق الكيميائية والطيفية .

