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STUDIES ON AROYL- AND ARYL-HYDRAZIDE DERIVATIVES FROM D-*glycero*-D-*gulo*-HEPTONO-1,4-LACTONE

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ABSTRACT

A series of aroyl- and aryl-hydrazide derivatives was prepared from D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**). The reactivity of the NH proton in these hydrazides, in terms of their dissociation constants (pK_a), was determined from their electronic spectra, and correlated to the Hammett σ values of the substituents. Comparable reactivities of the NH protons for the compounds, and the effect of the substituent, were studied by n.m.r. spectroscopy. Decomposition of the aroylhydrazides with copper(II) sulfate or nitrous acid resulted in the regeneration of **1**.

INTRODUCTION

Aldonic acid hydrazides[1,2] are useful derivatives for the characterization and purification of aldonic acids from their mixtures. Substituted-arylhydrazide derivatives from pentono- and hexono-lactones were studied[3], and the rate of the reaction was found to be dependent on the configuration of the aldonolactone, as well as on the aryl substituent on the hydrazine.

We have now prepared a series of aryl- and aroyl-hydrazides of a heptonic acid by reaction of D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**), obtained from D-glucose cyanohydrin[4], with the respective aroyl- and aryl-hydrazine. A comparative study on the ease of formation and properties of the aroyl- and aryl-hydrazides synthesized was made, to find out whether the aroylhydrazide can be used for the characterization and separation of mixtures of aldonic acids, analogously to arylhydrazides[3]. The relative acidities of the two imino protons in both types are discussed.

The respective arylhydrazides or aroyl hydrazides were prepared by refluxing the corresponding hydrazine derivative with the heptono-1,4-lactone **1** in the presence of a small proportion of acetic acid. The reaction of **1** with arylhydrazines is faster than with aroylhydrazines; for the former, the reaction was complete within 1–3 h, whereas, for the latter, 15–48 h were needed for complete reaction. This is attributed to the different basicity of the aryl- and aroyl-hydrazine derivatives; the former,

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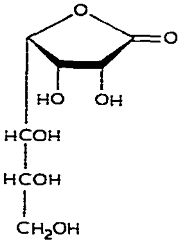
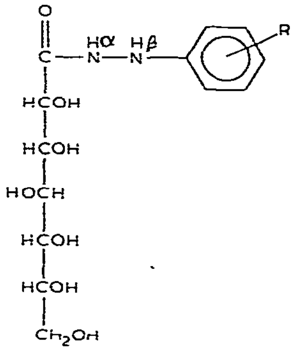
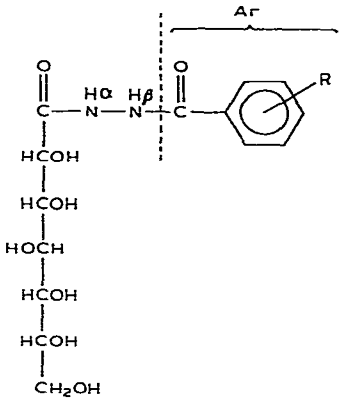


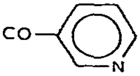
1



2 R = H
3 R = Cl-*p*
4 R = Br-*p*
5 R = I-*p*
6 R = NO_2-*p*
7 R = Me-*p*



8 R = H
9 R = Cl-*o*
10 R = Cl-*m*
11 R = Br-*o*
12 R = Br-*p*
13 R = NO_2-*p*
14 R = Me-*o*
15 R = Me-*m*
16 R = MeO-*p*
17 Ar = CH_2COPh
18 Ar = $CH_2COC_6H_4$-OMe-*p*
19 Ar = CO



20 Ar = SO_2Ph

being the more reactive, react faster. The reaction time and properties of **2–7** are recorded in Table I, and of **8–20**, in Table II.

The infrared (i.r.) absorption spectra of compounds **2–7** showed an amide band at 1665–1650 cm^{-1}. Compounds **8–20**, however, showed two amide bands, at 1660–1640 cm^{-1} and 1685–1670 cm^{-1}, corresponding to the sugar amide and the aromatic amide (anilide) groups, respectively.

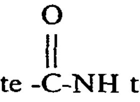
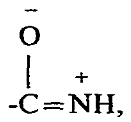
The ultraviolet absorption spectrum of the phenylhydrazide derivative **2** showed a weak absorption at 275 nm and a strong absorption at 232 nm. The latter absorption is characteristic for the hydrazide derivatives, and is due to the transition of the ground state  $\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-NH}$ to the exited state  $\text{-}\overset{\overset{\displaystyle \bar{O}}{|}}{C}=\overset{+}{N}H$, which is stabilized in polar solvents[5,6]. Arylhydrazides having an electron-release substituent (*e.g.*, **7**) showed a bathochromic shift of both bands. On the other hand, the ultraviolet absorption

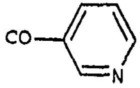
TABLE I

MICROANALYSES AND SPECTRAL DATA FOR D-*glycero*-D-*gulo*-HEPTONIC ARYLHYDRAZIDES

Compound No.	*R*	*Reflux (h)*	*Crystallization solvent*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{KBr} *CO (cm^{-1})*	λ_{max}	
						C	*H*	*N*	*C*	*H*	*N*		*cm^{-1}*	*log ε*
2	H	1.5	EtOH	170–172	$C_{13}H_{20}N_2O_7$	46.4	6.4	8.9	46.8	6.0	9.3	1660	232 275	3.2 2.6
3	Cl-*p*	3	EtOH	173–175	$C_{13}H_{19}ClN_2O_7$	44.5 (Cl, 10.1)	5.4	8.0	44.4 (Cl, 10.6)	5.4	8.2	1665	240 288 (sh)	3.2
4	Br-*p*	1	EtOH	182–184	$C_{13}H_{19}BrN_2O_7$	39.5 (Br, 20.5)	4.8	7.1	39.6 (Br, 20.1)	5.1	7.5	1660	247 285	3.3 2.5
5	I-*p*	1	EtOH (80%)	202–203	$C_{13}H_{19}IN_2O_7$	35.3	4.3	6.3	35.8	4.6	6.7	1670		
6	NO_2-*p*	3	EtOH	188–189	$C_{13}H_{19}N_3O_9$	41.2	5.3	11.6	41.3	5.3	11.5	1670		
7	Me-*p*	3	EtOH	173–175	$C_{14}H_{22}N_2O_7$	50.9	6.5		51.3	6.7		1665	238 285	3.2 2.6

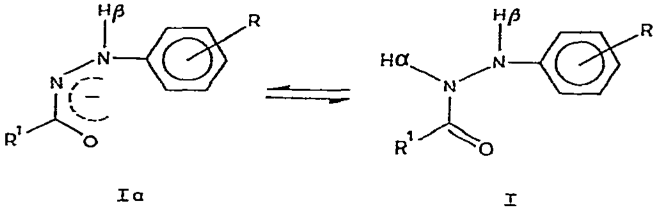
TABLE II

MICROANALYSES AND SPECTRAL DATA FOR D-*glycero*-D-*gulo*-HEPTONIC AROYLHYDRAZIDES

Compound No.	*R*	*Reflux (h)*	*Crystallization solvent*	*M.p. (degrees)*	*Molecular formula*	*Calculated (%)*			*Found (%)*			ν_{max}^{KBr} *CO* *(cm^{-1})*	λ_{max}	
						C	*H*	*N*	*C*	*H*	*N*		*cm^{-1}*	*log ε*
8	H	20	EtOH (90%)	190–192	$C_{14}H_{20}N_2O_8$	48.8	5.9	8.1	48.9	5.9	8.1	1690 1660	232 265 (sh)	3.3
9	Cl-*o*	15	EtOH (80%)	185–186	$C_{14}H_{19}ClN_2O_8$	44.4	5.0	7.4	44.8	5.4	7.6	1690 1660		
10	Cl-*m*	17	EtOH	165	$C_{14}H_{19}ClN_2O_8$	44.4	5.0	7.4	44.5	5.0	7.5	1690 1660	208 245	3.2 3.4
11	Br-*o*	17	MeOH (80%)	187	$C_{14}H_{19}BrN_2O_8$	39.7	4.5	6.6	39.8	4.3	7.0	1680 1650		
12	Br-*p*	15	EtOH (80%)	245–247	$C_{14}H_{19}BrN_2O_8$	39.7	4.5	6.6	39.6	4.6	7.0	1690 1640	220 250	3.0 3.2
13	NO$_2$-*p*	40	1-butanol	200–202	$C_{14}H_{19}N_3O_{10}$	43.2	4.9	10.8	43.0	5.4	10.8	1690 1640		
14	Me-*o*	16	EtOH (80%)	188–190	$C_{15}H_{22}N_2O_8$	50.3	6.2	7.8	50.2	6.3	7.8	1690 1645		
15	Me-*m*	16	MeOH	166–168	$C_{15}H_{22}N_2O_8$	50.3	6.2	7.8	50.5	5.8	7.9	1690 1640	217 235	3.3 3.4
16	MeO-*p*	20	EtOH (90%)	189–190	$C_{15}H_{22}N_2O_9$	48.1	5.9	7.5	48.1	5.9	7.4	1690 1650	210 255	3.3 3.5
17	CH$_2$COPh	24	EtOH (90%)	180–182	$C_{15}H_{22}N_2O_8$	50.3	6.2	7.8	50.2	5.8	7.7	1660		
18	CH$_2$CO-C$_6$H$_4$OMe-*p*	17	MeOH	190–192	$C_{16}H_{24}N_2O_9$	49.5	6.2	7.2	49.4	6.6	7.2	1685 1660		
19		48	EtOH	175–177	$C_{13}H_{19}N_3O_8$	45.2	5.5	12.2	45.7	5.3	12.6	1690 1660		
20	SO$_2$Ph	18	EtOH	178–180	$C_{13}H_{20}N_2O_8S$	42.9 (S, 8.8)	5.5	7.7	42.7 (S, 8.5)	5.5	7.8	1685		

spectrum of the corresponding benzoylhydrazide derivative (**8**) showed the two absorption bands at 270 and 232 nm. The latter absorption is common for aryl- and aroyl-hydrazides.

The ultraviolet absorption spectra of both types of hydrazide were sensitive to variation in pH within the pH range of 4–13. For the arylhydrazides, gradual increase in the pH resulted in gradual increase in the intensity of the long-wavelength absorption, with the formation of one isosbestic point, indicating the presence of one equilibrium species Ia $\rightleftharpoons$ I (see Scheme 1). Compounds **2**, **3**, and **4** showed the isosbestic points at 242, 253, and 249 nm, respectively. This phenomenon is reversible, and, on acidifying the solution with acetic acid, the spectra return to that of the neutral solution. The pK_a values for these compounds were determined by using the



I = Compounds 2 − 7
R = Substituent group
R¹ = D-*glycero*-D-*gulo*-heptono group

Scheme 1

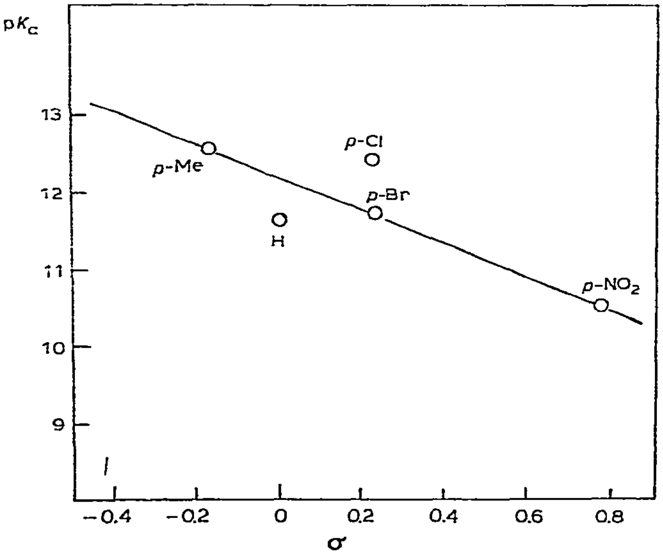


Fig. 1. The Hammett correlation of the dissociation constants of the arylhydrazides.

TABLE III

CHANGE OF THE pK_a VALUE OF AROYL- AND ARYL-HYDRAZIDES WITH THE σ CONSTANT OF THE SUBSTITUENT

Compound	pK_a	σ
2	11.6	0.000
3	12.4	+0.227
4	11.7	+0.232
6	10.5	+0.778
7	12.5	−0.170
8	9.1	0.000
10	12.8	+0.373
12	10.1	+0.230
15	9.15	−0.069
16	9.4	−0.268

TABLE IV

CHEMICAL SHIFT (δ) OF SOME AROYL- AND ARYL-HYDRAZIDE DERIVATIVES

Compound	*Chemical shift (p.p.m.)*	
	NHα	*NHβ*
2	9.50	7.50
6	10.03	9.02
8	10.02	10.50
9	9.67	10.67
13	9.93	10.80
15	10.02	10.50
16	9.80	10.30

modified, limiting-absorbance method[7,8]. Plotting of pK_a values against the Hammett constants gave a straight line (see Fig. 1) having a slope of —0.210. The linear, Hammett relation confirmed[9] the presence of one proton susceptible to abstraction by the base. The small σ values (see Table III) indicate the weak interaction due to absence of conjugation between the respective substituent at the aryl group and the negatively charged oxygen atom. These results were supported by n.m.r.-spectral results, which showed NHα at lower field than NHβ for compounds **2**–**7**, even for the strongly electron-attracting, nitro substituent of compound **6** (see Table IV).

Similarly, the aroylhydrazides were also sensitive to variation in pH; the high-wavelength absorption (270 nm) showed gradual increase in intensity with gradual increase in the pH (see Fig. 2). The spectra were characterized by the presence of two isosbestic points. Compound **8** showed the isosbestic points at 247, 225 nm, and **12**, at 258, 243 nm. This phenomenon indicates the presence of more than one equilibrium between the ionic species in solution, which arises by the ionization of either NHα or

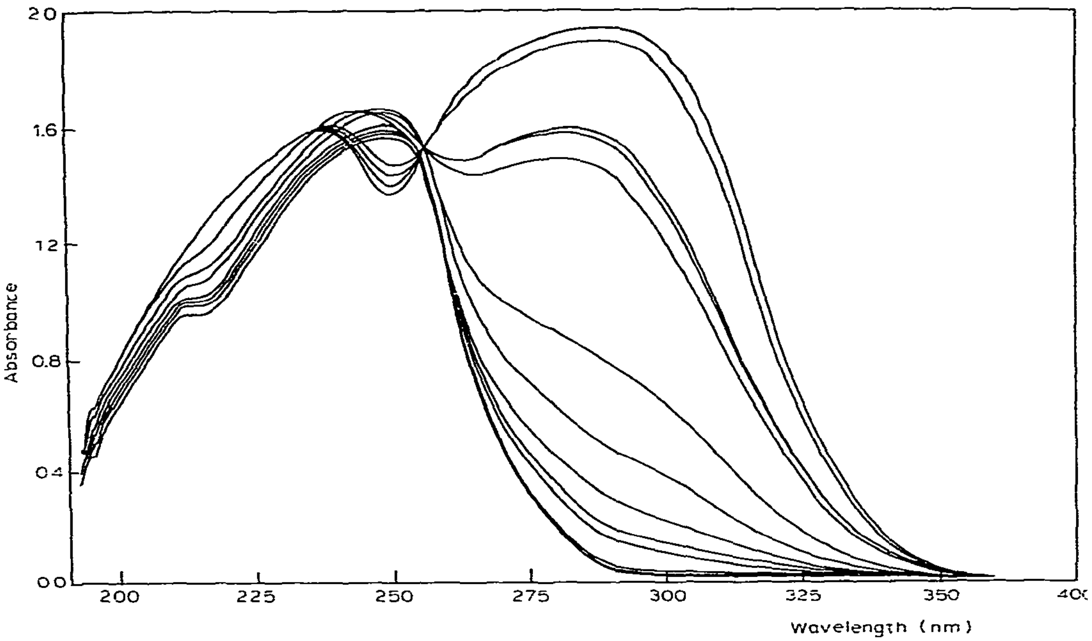


Fig. 2. Effect of pH on the electronic spectrum of D-*glycero*-D-*gulo*-heptonic *p*-bromobenzoylhydrazide.

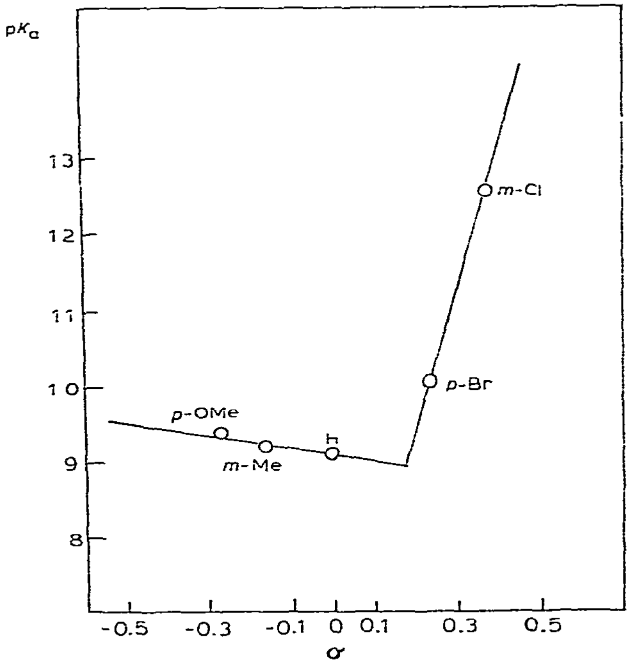
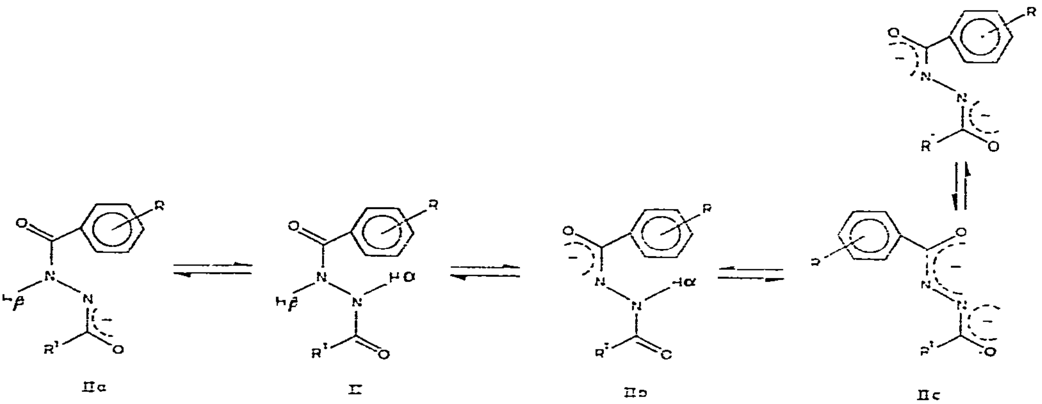


Fig. 3. The Hammett correlation of the dissociation constant of the aroylhydrazides.



II = compounds 8-20
R = Substituent group
R' = D-*glycero*-D-*gulo*-Heptono group

Scheme 2

NHβ or both; IIa $\rightleftharpoons$ II $\rightleftharpoons$ IIb $\rightleftharpoons$ IIc (see Scheme 2). The ionization of NHβ is more facilitated by the adjacent aroyl group, as supported by its appearance at low magnetic field (see Table II).

Plotting pK_a values for compounds **8**, **10**, **12**, **15**, and **16** against the Hammett σ constants of the substituents gave a V-shaped relationship (see Fig. 3). Electron-donating substituents showed a negative slope (σ -1.26) and electron-attracting substituents showed a positive value (σ $+19.18$).

The n.m.r. spectra of both types of hydrazide showed the imino protons at low magnetic field as broad peaks exchangeable with deuterium by deuteration with D_2O or CD_3CO_2D. The imino proton NHα appeared at δ 9.50–10.02, for both types of hydrazide, indicating the chemical equivalence of the NHα proton of the hydrazides. Electron attraction or electron release did not show a large change in the chemical shift of this imino proton. On the other hand, NHβ for compounds **2–7** appeared at higher field than NHα, and was sensitive to the aryl substituent as a result of the resonance effect. Contrariwise, the aroylhydrazides showed NHβ at lower field than NHα; this may be explained by the anisotropic effect of both the carbonyl and the phenyl group of the aroyl group. Similarly, NHβ for compounds **8–20** was shifted downfield compared to that of compounds **2–7**. Substituents on the aroyl group showed little effect on the chemical shift of NHβ, due to the absence of conjugation between the substituent and NHβ. The small effect observed is due to the inductive effect of the substituent. The aromatic protons of compounds **2–20** were found at δ 6.7–8.08, and, at higher field, there was a doublet of one-proton intensity at δ 5.5–5.7, exchangeable by deuteration, assigned to the hydroxyl group α to the hydrazide residue. The rest of the sugar protons appeared as a multiplet of 12-proton intensity at δ 3.3–4.9 which, by deuteration, collapsed into a multiplet of 7-proton intensity.

Although formed after a longer reaction-time than that for the aryl analogs, the aroylhydrazide derivatives are more sensitive to acid hydrolysis. Like the arylhydrazide analogs[1,2,10], the aroylhydrazides are decomposed by copper(II) sulfate, or nitrous acid, with the regeneration of the precursor aldonolactone. These properties make these compounds useful derivatives for the separation and characterization of aldonolactones.

EXPERIMENTAL

General. — Melting points were determined with a Kofler-block apparatus and are uncorrected. I.r. spectra were recorded with a Unicam SP-200 and a Beckman IR-33 instrument. U.v. spectra were recorded, for solutions in a buffer, with a Unicam SP-800 spectrometer. N.m.r. spectra were recorded with Varian A (60 MHz) instrument. Microanalyses were performed in the Chemistry Department, Faculty of Science, Cairo University, Cairo. Egypt.

D-glycero-D-gulo-*Heptonic arylhydrazides.* — A solution of D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**, 0.01 mol) in water (5 mL) and acetic acid (3 drops) was treated with a hot, alcoholic solution of the arylhydrazine (11 mmol), and the mixture was boiled under reflux for 1–3 h, and cooled. The crystals that separated were filtered off, and recrystallized from ethanol, or dilute ethanol (see Table I).

D-glycero-D-gulo-*Heptonic aroylhydrazides.* — A solution of **1** (0.01 mol) in water (3–5 mL) was treated with a solution of the aroylhydrazine (12 mmol) and 3 drops of acetic acid in alcohol (100 mL), and boiled under reflux for 15–48 h. The crystals obtained were recrystallized from 90% ethanol (see Table II).

Effect of copper(II) sulfate on D-glycero-D-gulo-*heptonic benzoylhydrazide* (**8**). — A solution of **8** (2.5 g) in water (25 mL) was treated with a solution of copper(II) sulfate[10] (2 g) in water (25 mL), and boiled under reflux for 5 h. The copper ions were removed by bubbling hydrogen sulfide through the cooled solution, and the suspension was filtered. The sulfate ions were then removed by stirring with barium carbonate, and the suspension was filtered. The filtrate was evaporated under diminished pressure to a thin syrup which was dissolved in water, and the product lactonized in a current of air. D-*glycero*-D-*gulo*-Heptono-1,4-lactone (**1**) separated; it was filtered off, washed with alcohol, and dried; m.p. and mixed m.p. 153–155°.

Effect of nitrous acid on D-glycero-D-gulo-*heptonic benzoylhydrazide* (**8**). — Into a solution of **8** (2 g) in a mixture of water (5 mL) and concentrated hydrochloric acid (1 mL) was bubbled a stream of nitrous anhydride[1] for 3 h, the temperature being kept at 15–20° by cooling in ice. The solution was made alkaline by addition of 50% potassium hydroxide solution, and evaporated under diminished pressure to a syrup. Absolute ethanol (10 mL) was added, the solution was acidified with hydrochloric acid, and the potassium chloride that separated was filtered off, and washed with ethanol. The filtrate and washings were combined, and evaporated under diminished pressure to a syrup; traces of water were removed by repeatedly dissolving in absolute ethanol and evaporating to a syrup, and this was nucleated and kept in a refrigerator. The solid obtained was filtered off, and successively washed with alcohol and ether; m.p. and mixed m.p. with an authentic sample of **1**, 152–155°.

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