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Derivatives of Isoniazid (II)
Esters of Salicylideneisonicotinylhydrazide

İsoniazid Türevleri (II)
Salisilidenisonikotinilhidrazid Esterleri

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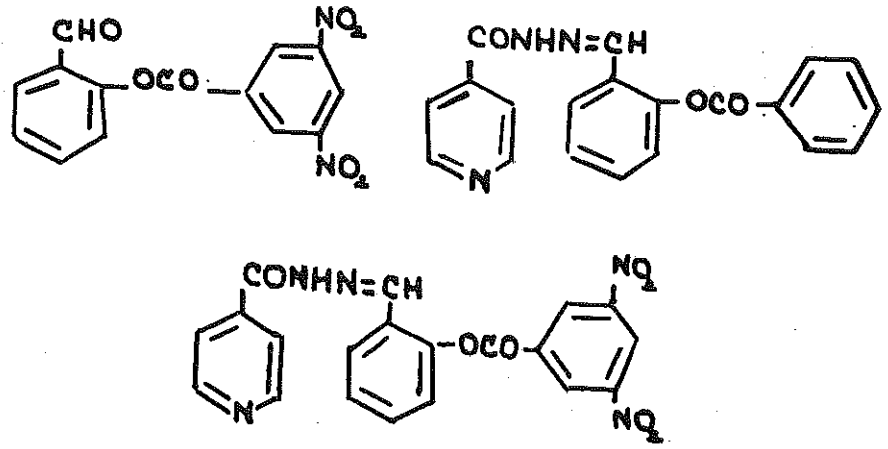
In a previous paper(1), two new esters of vanillydenisonicotinylhydrazide which were prepared by heating isoniazid and phenolic esters of vanillin in ethanol, were reported.

In the present investigation we synthesized a new ester of salicylaldehyde,2-(3′,5′-dinitrobenzoyloxy) benzaldehyde(I), and three isonicotinyl hydrazones,2-benzoyloxybenzylidenisonicotinylhydrazide(II), 2-(3′,5′-dinitrobenzoyloxy)benzylidenisonicotinylhydrazide(III), 2-benzensulfonyloxybenzylideneisonicotinylhydrazide(IV), and studied the color reactions and spectral characteristics of these compounds.



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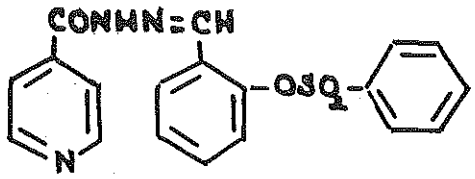

The hydrazones were obtained by the condensation of isoniazid with the esters of salisylaldehyde. These compounds gave no reaction of free hydrazide and phenolic groups, were the reaction of pyridine ring with 1-chloro-2,4-dinitrobenzene(2-5) and the reaction of hydrazide-hydrazone group with sodium nitroprusside(6-8), phosphomolibdic acid and potassium dichromate(6) were positive.

The alkaline hydrolysis effected both of the esters of salicylideneisonicotinhylhydrazide and of the hydrazone group as in the case of vanilidenisonicotinylhydrazide esters.

The UV curves of all the three hydrazones have maximum absorptions near 300 mμ and these were in accordance with the values given by Grammaticakis(9). In IR spectra the caracteristic absorption bands for aromatic and heterocyclic rings, substition position, hydrazide and hydrazone groups, ester group, nitro group (in dinitrobenzoyl ester) and SO_2-group (in benzensulfonyl ester) were found. In the NMR spectra of dinitrobenzoyl and benzensulfonyl esters, the hydrogen belonging to aromatic and heterocyclic rings were stated beside that of hydrazine and aldehyde groups.

EXPERIMENTAL

2-(3′,5′-Dinitrobenzoyloxy)benzaldehyde(I)

4.6 g (0.02 mol) of 3,5-dinitrobenzoyl chloride is added portionwise to a stirred solution of 2.44 g (0.02 mol) salisylaldehyde in 10 ml of aqueous potassium hydroxyde. After the addition of acid chloride is completed, the stirring is continued for 30 minutes. The precipitated ester is filtered and washed first with a small amount of diluted solution of potassium hydroxyde followed with distilled water, until the washings gave neutral reaction, dried and crystallized from benzene. The yield was 3.2 g (50%). White microcrystalline powder, m.p. 143°C, soluble in acetone, slightly soluble in cold methanol and more soluble

in hot methanol, ethanol, benzene and petroleum ether; insoluble in water and ether. λ_{max}^{EtOH} 253 mμ (Σ 19 100), 326 mμ (Σ 3 660).

The relation between the absorbencies, and concentrations is linear and obeys the Beer's law for the solution containing 1.1-6 mg in 100 ml.

It reduces the ammoniacal silver nitrat solution and Fehlings reagent, gives an orange color with p-nitrophenylhydrazine and 2,4-dinitrophenylhydrazine in cold and an orange precipitate when heated for 30 minutes; a cherry red color is developped with 2,3,5-triphenyltetrazolium chloride in alkaline medium. No color with ferric chloride solution is obtained.

Thin layer chromatography was performed on Silicagel $HF_{254+366}$ Merck 0.25 mm; with the solvent systems (S_1) methanol-ethyl acetate (10 : 90) and (S_2) chloroform-ethyl methyl ketone (50 : 100); (development time : 35 minutes; temparature : 18°C). The Rf values were 0.70 and 0.71 respectively.

Hydrolysis. 0.5 g of substance was hydrolysed with 5 ml of 0.5 N ethanolic potassium hydroxide by heating for 30 minutes on water

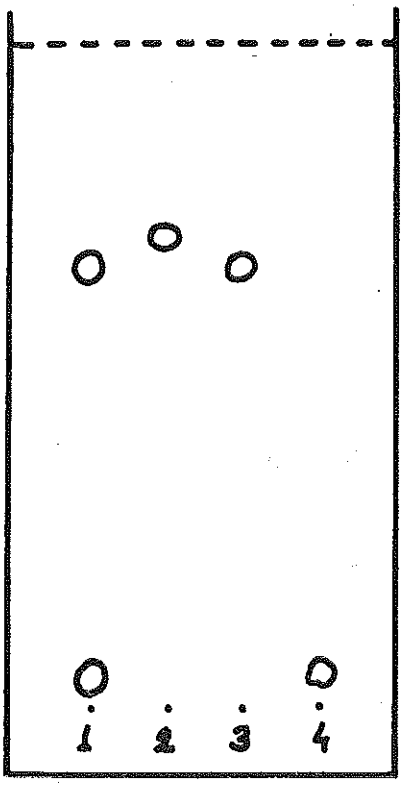

Fig. 1. Chromatogramme of tne hydrolysate : 1. hydrolysate, 2. comp. I Rf: 0.71, 3. salicylaldehyde Rf: 0.65, 4. dinitrobenzoic acid Rf: 0.05 (S_2).

bath. The hydrolysate gave a purple color with a 5% solution of ferric chloride after acidified with diluted sulfuric acid.

The hydrolysation product was chromatographed on Silica gel $HF_{254+366}$ together with the salicylaldehyde and 3,5-dinitrobenzoic acid; the hydrolysate gave two spots having the same Rf values as the test substances (Fig. 1).

The IR spectrum of the compound in KBr was taken with a Perkin - Elmer Spectrophotometer; the following absorption bands were observed: at 1600, 1578, 1482 and 1450 cm^{-1} the carbon double band of aromatic ring; at 1760, 1272, 1145 cm^{-1} ester group; at 1545 and 1345 cm^{-1} aromatic nitro group; at 1692 and 3100 cm^{-1} 1,3,5-trisubstituted benzene (Fig. 2).

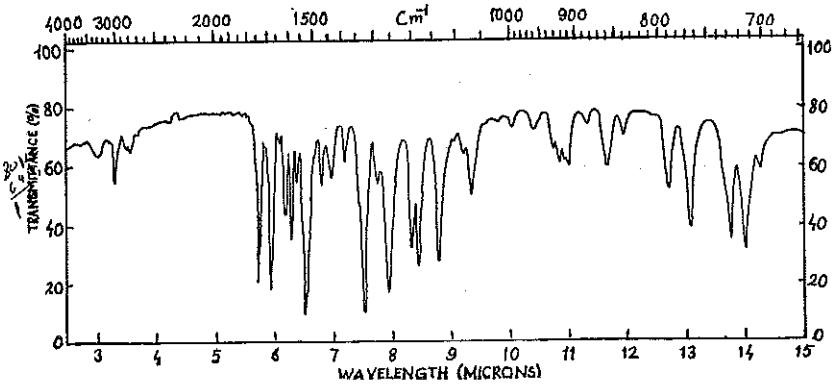

Fig. 2. IR spectrum of the compound I.

The NMR curve was taken with a Varian Model A 60 in $CDCl_3$. The caracteristic peaks are: 7.37 ppm the ring hydrogenes of salicylaldehyde, 8.62 ppm the ring hydrogenes of dinitrobenzoyl group and 8.95 ppm the hydrogen of aldehyde group.

Anal. Calcd. for $C_{14}H_8N_2O_7$: C, 53.12; H, 2.55; N, 8.85 Found; C, 52.20; H, 2.45; N, 9.17.

2-Benzoyloxybenzylideneisonicotinylhydrazide (II)

A solution of 2.26 g (0.01 mol) of benzoyloxybenzaldehyde and 1.64 g (0.012 mol) of isoniazid in 50 ml ethanol were refluxed on a water bath for 30 minutes. The reaction mixture was concentrated and than

cooled, the precipitate was filtered and washed first with water, than with a small amount of ethanol and finally with ether to remove the unreacted starting materials, dried and purified by recrystalization from ethanol. The yield was 2.9 g (80%).

White needles, m.p. 213°C. Soluble in methanol, ethanol, acetone, chloroform, dilute acid and alkalie hydroxyde; slightly soluble in propylene glycol and glycerol; insoluble in water, ether, petroleum ether and benzene. λ_{max}^{EtOH} 230 mμ (Σ 23 360), 303 mμ (Σ 21 680).

It gives a rose red color with 2.5% solution of sodium nitroprusside in alkaline medium, a blue color, when heated with a 10% solution of phosphomolibdic acid and a blue color with cobaltous thiocyanate solution; no color with ferric chloride and p-dimethylaminobenzaldehyde.

The Rf values were 0.42 and 0.32 respectively at the system S_1 and S_2 when chromatographed on Silica gel $HF_{254+366}$.

Hydrolysis. 0.5 g was hydrolysed with 5 ml of 0.5 N ethanolic potassium hydroxyde, by heating on a water bath for 30 minutes. Benzoic acid, salisylic aldehyde, and isoniazid were identified in hydrolysate using thin layer chromatography.

The following absorption bands were observed in the IR spectrum of the compound (in KBr): 1605, 1570, 1485 and 1450 cm^{-1}, the —C=C— of aromatic and pyridine rings; 1730, 1255, 1105^{-1}, ester 3160 and 1545 cm^{-1}, N-H; 1665 cm^{-1}, C-O; 1325 cm^{-1}, C-N; 1650 cm^{-}, —CH=N—; 838 cm^{-1}, monosubstituted pyridine; 730 cm^{-1}, o-disubstituted benzene; 750 and 705 cm^{-1} monosubstituted benzene (Fig. 3).

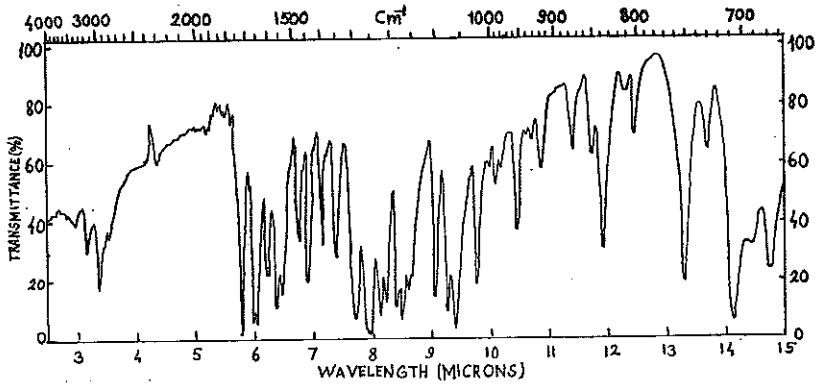

Fig. 3. IR spectrum of the compound II.

Anal. Calcd. for $C_{20}H_{15}N_3O_3$: C, 69.55; H, 4.37; N, 12.16; Found: C, 69.50; H, 4.50; N, 12.06.

2-(3',5'-Dinitrobenzoyloxy)benzylidenisonicotinylhydrazide (III)

This compound was obtained from 3.16 g (0.01 mol) of 2-(3,5-dinitrobenzoyloxy)benzaldehyde and 1.64 g (0.012 mol) of isoniazid, using the same technique as described for comp. II, with a yield of 3.4 g (78 %), after recrystallizing from acetone. Creamy white needles, m.p. 218-19°C. Slightly soluble in methanol, ethanol and acetone; soluble in dilute acids and alkalie hydroxydes; insoluble in water, ether, petroleum ether and benzene. λ_{max}^{EtOH} 300 $m\mu$ (Σ 19 960). The relation between the absorbancies and the concentrations is linear and the systems obey the Beer's law for the solution containing 0.1-1.6 mg in 100 ml. It gives the same color reactions as substance II.

The Rf values in thin layer chromatography were 0.44 and 0.32 (adsorbent Silica gel $HF_{254+366}$ solvent systems S_1 and S_2).

Hydrolysis. After hydrolyzing 0.5 g of the substance as described in comp. I, the 3,5-dinitrobenzoic acid, salicylic aldehyde and isoniazid were identified in the hydrolysate.

The following absorption bands were observed in the IR spectrum; 1605, 1587, 1490, 1442 cm^{-1} the C=C bands of aromatic and pyridine rings; 1725, 1210, 1150 cm^{-1} ester; 3300 cm^{-1} —N-H; 1650 cm^{-1} —C=O; 1690 cm^{-1} —CH=N—; 1535 cm^{-1} o-disubstituted benzene; 680 cm^{-1} 1,3,5-trisubstituted benzene (Fig. 4).

In the NMR spectrum of the substance in DMSO, at 7.68 ppm the ring hydrogens of salicylaldehyde at 8.35 ppm the ring hydrogens of salicylaldehyde; at 8.35 ppm the ring hydrogens of dinitrobenzoyl

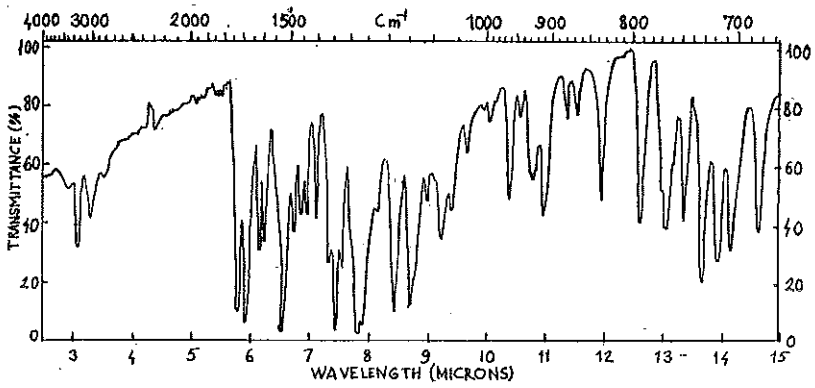

Fig. 4. IR spectrum of the compound III.

group; at 8.42 and 7.84 ppm the hydrogens of pyridine ring and at 8.84 ppm the hydrogen of hydrazone group were found.

Anal. Calcd. for $C_{20}H_{13}N_5O_7$: C, 55.17; H, 3.19; N, 16.08. Found; C, 55.10; H, 2.83; N, 16.31.

2-Benzenesulfonyloxybenzylideneisonicotinylhydrazide (IV)

This compound was prepared from 2.62 g (0.01 mol) of 2-benzensulfonyloxybenzaldehyde and 1.64 g (0.012 mol) of isoniazid using the same method as described for the substance II and purified by recrystallization from ethanol. The yield was 3 g (78%). White needles, m.p. 155-56°C. Soluble in methanol, ethanol and acetone, dilute acids and alkalie hydroxides; more soluble in hot metanol, ethanol and petroleum ether and benzen. λ_{max}^{EtOH} 300 mμ (Σ 21 370). The relation between the absorbancies and the concentrations is linear and the system obeys Beer's law for the solution containing 0.2-1.47 mg in 100 ml.

The Rf values in thin layer chromatography were 0.41 and 0.33 respectively. (Adsorbent Silica gel $HF_{254+366}$ solvent systems S_1 and S_2).

The hydrolysis of this substance yields benzensulfonic acid, salicylaldehyde and isoniazid.

The IR spectrum of this substance (in KBr) has the following bands: 1605, 1478, 1450 cm^{-1}, —C=C— groups of aromatic and heterocyclic rings; 1190 and 1158 cm^{-1} sulfonic acid ester; 1600 cm^{-1} —CH=N— group; 1650 cm^{-1} C=O group, 1370 cm^{-1} C-N, 3220 and 1550 cm^{-1} N=H bands of hydrazide group; 840 cm^{-1} monosubstituted pyridine; 780 and 678 cm^{-1} monosubstituted benzene; 730 cm^{-1} o-disubstituted benzene (Fig. 5).

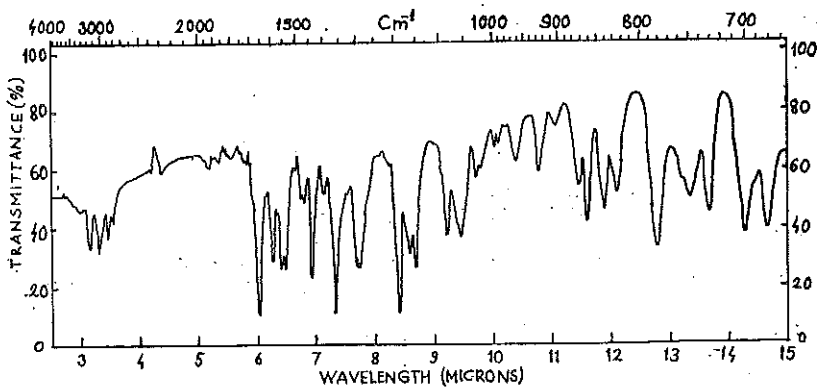

Fig. 5. IR spectrum of the compound IV.

In the NMR spectrum of the substance in $CDCl_3$ at ca. 7.5 ppm the ring hydrogenes of benzene sulfonyl group; at 7.73 ppm the ring hydrogenes of salicylaldehyde, at 7.90 and 7.95 ppm the hydrogenes of pyridine ring; at 9.90 ppm the hydrogene of —CH=N— group found.

Anal. Calcd. for $C_{19}H_{15}N_3O_4S$: C, 59.83; H, 3.96; N, 11.01; S, 8.40. Found; C, 59.66; H, 4.02; N, 11.15; S, 8.31.

SUMMARY

A new ester of salicylaldehyde, 2-(3′,5′-dinitrobenzoyloxy) benzaldehyde (I) is prepared by treating salicylaldehyde with the acid chloride in alkaline media at room temparature. Three isonicotinylhydrazones, 2-benzoyloxybenzilideneisonicotinylhydrazide (II), 2-(3′,5′-dinitrobenzoyloxy) benzilideneisonicotinylhydrazide (III) and 2-benzenesulfonyloxybenzilideneisonicotinylhydrazide (IV), are synthesized by heating isoniazide and phenolic esters of salicylaldehyde in ethanol. Their Rf values, and C, H and N were determinated, UV, IR and NMR spectra were studied.

ÖZET

Salisilaldehidin alkali vasatta, oda temparatüründe asid klorürü ile muamelesi suretiyle yeni bir salisilaldehid esteri, ayrıca 2-(3′,5′-dinitrobenzyloksi) benzaldehid (I) ve isoniazidin salisilaldehid fenolik esterleri ile etanollü vasatta ısıtılması suretiyle üç yeni isonikotinilhidrazon, 2-benzoiloksibenzilidenisonikotinilhidrazid (II), 2-(3′,5′-dinitrobenzoiloksi) benzilidenisonikotinilhidrazid (III), 2-benzensulfoniloksibenzilidenisonikotinilhidrazid (IV) hazırlanmıştır. Bu dört maddenin Rf değerleri ile C, H ve N yüzdeleri tayin edilmiş ve UV, IR, NMR spektrumları incelenmiştir.

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