Condensation Products of Isomeric Pyridine Carboxylic Acid Hydrazides with Ninhydrin

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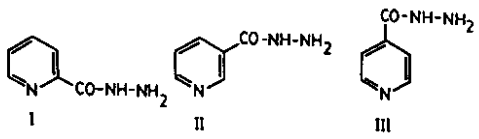
Summary: The condensation products of pyridine-2-carboxylic acid hydrazide (I) and pyridine-3-carboxylic acid hydrazide (II) with ninhydrin (VII) have been isolated. Their structures as VIII and IX, respectively, have been established on the basis of their IR, visible, PMR and mass spectral data. A mechanism for the condensation reaction has also been proposed.

Introduction

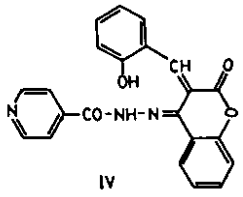
Although the three isomeric pyridine carboxylic acid hydrazides, pyridine-2-carboxylic acid hydrazide(I), pyridine-3- carboxylic acid hydrazide (II) and pyridine-4-carboxylic acid hydrazide (III) possess significant physiological activities[1-4], yet their use as effective drugs remains limited because of their relatively high toxicities[5,6]. In order to overcome the problem caused by the toxicities of the hydrazides, attempts have been made to prepare such derivatives of the isomeric pyridine carboxylic acid hydrazides which are relatively less toxic but possess the same level of physiological activites as the parent hydrazide. Thus, a wide variety of their derivatives have been prepared and screened out for different types of physiological activities. In this connection, the mono-acetyl derivatives of the hydrazides I and II have been found[7] to inhibit neoplasms. Similarly, some hydrazones derived from III have been reported to possess different types of physiological activites; hydrazone IV has been reported to be antituberculotic as well as antitumer[8] and hydrazone V showed high activity against leprosy[9] and hypertension[10]. It has been established that some hydrazones prepared by the reaction of III with certain carbonyl compounds show comparable antituberculotic activity to that of III but are less toxic than the parent hydrazide[11]. In view of these facts, it is desirable to prepare and screen out new hydrazone derivatives of isomeric pyridine carboxylic acid hydrazides. In this connection, the isolation of hydrazone VI by the reaction of III with ninhydrin VII has already been reported[12]. We have now successfully carried out the preparation and characterization of the isomeric hydrazones VIII and IX by the reaction of VII with I and II respectively. In this article the results of these studies are reported.

Results and Discussion

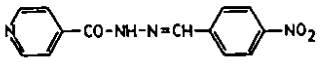
In the present work, the condensation reactions of I and II with VII under both neutral and alkaline aqueous conditions were studied as represented by the equations (1) and (2). The condensation reaction occurred under neutral as well as basic conditions. However, the reaction was found to be much slower under the neutral as compared to the basic conditions. Thus, when the reaction was carried out under neutral reaction conditions for three hours, only 29.8% of VIII and 21.3% of IX could be isolated, while under basic conditions, good yields of VIII (80.9%) and IX (59.5%) were achieved even after half an hour stirring. This observation is in line with the earlier findings[13a] that such condensation reactions are base-catalysed and is discussed later in the light of the reaction mechanism. The higher yield based on the isolated VIII as compared to IX is considered mainly due to the fact that the former VIII is insoluble whereas the later IX is moderately soluble in the reaction medium. Thus, whereas VIII precipitated out almost completely on its formation, IX was only partly precipitated and had to be isolated by a combination of filtration and solvent extraction. The purity of both the isolated hydrazones VIII and IX was established by TLC technique; on a silica plate, in three different solvent systems, ethanol-petroleum ether (1:4), ethanol-benzene (1:1) and acetone-petroleum ether (1:4), each of the two isolated compounds yielded a single spot with R_f value



I II III



IV



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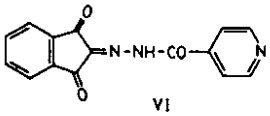

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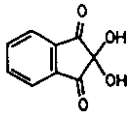
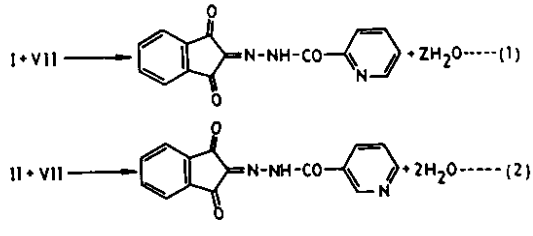


VII

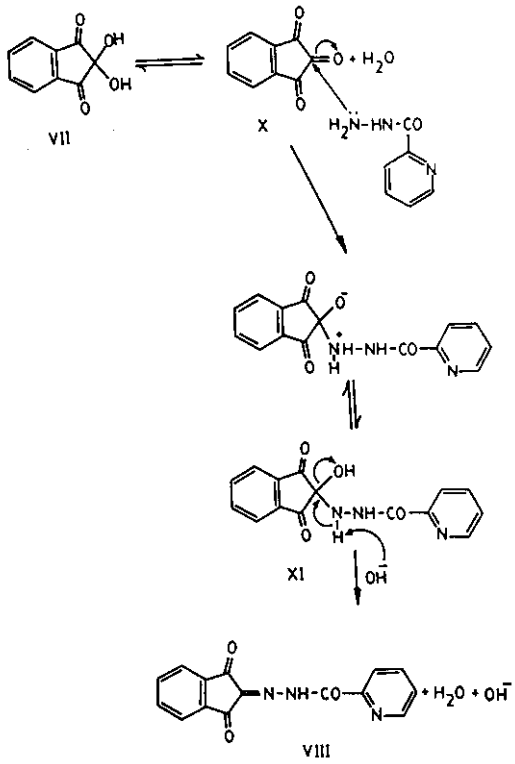
different than that of either ninhydrin or the corresponding hydrazide. As far as the solubilities of the two hydrazones are concerned VIII was found to be soluble in dimethylsulfoxide and acetonitrile and moderately soluble in methanol, ethanol, acetone, chloreform, ethyl acetate and benzene, and IX was found to be soluble in acetone, chloroform, dimethylsulfoxide, ethyl acetate and partially soluble in water, methanol, ethanol, benzene and acetonitrile.

The structure of VIII was established on the basis of the following spectral data. In chloroform solution, it exhibited a strong absorption in the visible reagion with the maximum absorption at 435 nm. Since the compound is insoluble in water, it was not possible to record the visible spectrum of its aqueous solution. The IR spectrum (KBr) displayed peaks of moderate intensities at 3200 and 3080 cm^{-1}, and peaks of strong intensities at 1720, 1700, 1675 and 1585 cm^{-1}. However, the strongest absorption was observed at 1675 cm^{-1} similar to that observed earlier[12] in the IR spectrum of the condensation product (VI) obtained by the reaction of III with VII. In the mass spectrum, the molecular ion peak was observed at m/z 279. Other important abundant peaks were observed at m/z 278, 223, 173, 145, 106 and 78. The PMR spectrum of VIII in d_6-acetone exhibited a one-proton signal at δ 9.9, a one-proton doublet at δ 8.7, two-proton multiplet at δ 8.0, one-proton triplet at δ 7.8 in addition to a four-proton multiplet at δ 7.2-7.5

The structure of IX was also established on the basis of its observed spectral data. The visible spectrum of IX, in chloroform solution, exhibited a strong absorption at 430 nm. The IR spectrum (KBr) displayed peaks of moderate intensities at 3220 and 3080 cm^{-1} in addition to peaks of high intensities at 1715, 1690, 1670 and 1580 cm^{-1}. In this case also, the peak at 1670 cm^{-1} was found to be the most intense. In the mass spectrum, the molecular ion peak was observed at m/z 279. This corresponded to molecular formula $C_{15}H_9N_3O_3$. The fragmentation pattern was found similar to that of isomeric VIII. However, as expected, the PMR spectrum of IX in d- chloroform was found different from that of VIII. It exhibited a one-proton signal at δ 10.0, a one-proton singlet at δ 9.1, a one-proton doublet at δ 8.7, a one-proton doublet at δ8.2, a one- proton triplet at δ 7.8 and a four-proton multiplet at δ 7.3-7.6.



As far as the reaction mechanism of the condensation reaction is concerned, the Scheme illustrates the proposed mechanism for the reaction of I with VII. Under neutral reaction conditions, in the initial stage of the reaction, the terminal nitrogen atom of the hydrazide, being the most reactive site, attacks carbon-2 of indane-1,2,3-trione (X) which exists as the dehydrated form ofVII. This results in the formation of a carbonylamine (XI) which undergoes rapid dehydration catalysed by base present in the later stage of the reaction. The



SCHEME

lower yields of the condensation products VIII and IX obtained under neutral conditions in a relatively longer reaction time would provide an evidence for this effect. It has been suggested that in this type of reaction, in order to prevent further condensation of the initially formed hydrazone with the carbonyl compound, it is necessary to employ a slight molar excess of the hydrazide and carry out the reaction under basic conditions[13a]. In the present work a slight molar excess of the two hydrazides relative to that of ninhydrid was used. Also, the yields of the respective condensation products were achieved higher under the basic reaction conditions as compared to the neutral reaction conditions. It may be pointed out that in such reactions the acidic reaction conditions are known to encourage undesirable further condensation[13b].

Experimental

The melting points were not corrected and were observed by using a Gallenkamp melting point apparatus. The IR spectra were recorded on a Pye-Unicam infrared spectrophotometer model SP-1000. For recording the visible spectra, a Hitachi model 220-S spectrophotometer was used.

Substrates and Reagents: Pyridine-2-carboxylic acid, ninhydrin, hydrazine hydrate, sodium hydroxide and anhydrous sodium sulphate were obtained from E. Merck. Pyridine-3-carboxylic acid, methanol and chloroform were supplied by Fluka. All commercially obtained reagents were used as such without further purification. Pyridine-2- carboxylic acid hydrazide (I) was prepared by the method[14] involving reaction of pyridine-2-carboxylic acid with hydrazine hydrate; yield 81%, m.p. 98-99°, lit.m.p[3]. 98-100°. Pyridine-3- carboxylic acid hydrazide (II) was prepared from pyridine-3-carboxylic acid by the same method as reported[15] for the preparation of pyridine-4-carboxylic acid hydrazide from the corresponding acid. In the present case pyridine-3-carboxylic acid (40g) was refluxed with hydrazine hydrate, (80%, 60ml) for six hours. The reaction mixture was then cooled and allowed to solidify. The crude solid thus obtained was recrystallized from methanol; yield 72%, m.p. 161-162°, lit.m.p[16]. 161-162°.

Reaction of Isomeric Hydrazides with Ninhydrin: The general method followed for the condensation reaction of I with VII and II with VII was, in principle, the same as reported for the condensation of III with VII[12]. However, the reaction, in each case, was carried out under neutral as well as basic conditions; it was observed that the reaction of both the isomeric hydrazides, I and II, was much more facile under the basic conditions as compared to the reaction under neutral conditions. The procedure for isolation of hydrazones VIII and IX had to be slightly modified in view of the difference in the solubilities of the condensation products VI, VIII and IX. This is briefly described below:

Preparation of VIII by the reaction of I with VII: I (0.60g, 0.0044 mole) and VII (0.75g, 0.0042 mole) were separately dissolved in distilled water (120ml each). The aqueous solution of VII was added to the constantly stirred solution of I. The mixture was then made basic by dropwise addition of aqueous sodium hydroxide solution (0.1M) to a pH of about 9 as indicated by the pH-paper. At this stage an orange-yellow precipate separated immediately. The reaction mixture was stirred for another five minutes. The precipitate was then filtered, washed with water (about 60ml) and recrystallized with methanol to yield bright yellow fluffy crystals of VIII; yield 0.95g (80.9%), m.p. 277°.

Found: C,65.05; H,3.56; N,14.90%. $C_{15}H_9N_3O_3$ requires C, 64.51; H, 3.22; N,15.05%. The reaction was also carried out under neutral conditions i.e. without addition of sodium hydroxide solution. In this case, the stirring time of the reaction mixture was increased to three hours. However only 29.8% yield ofVIII could be isolated.

Preparation of IX by the reaction of II with VII: In this case, also, II (0.60g, 0.0044 mole) and VII (0.75g, 0.0042 mole) were separately dissolved in distilled water (120ml each). Both the aqueous solutions were mixed in the same manner as described above for the reaction of I. The pH of the reaction mixture was adjusted to about 9 (as indicated by the pH-paper) by dropwise addition of aqueous sodium hydroxide solution (0.1M). The reaction mixture was then stirred for another ten minutes during which time a yellow precipitate started appearing. Completion of the precipitation was allowed by cooling the reaction mixture in an ice-bath for about fifteen minutes. The yellow precipitate was then filtered and washed with cold water (25ml). In view of the relatively small amount of the precipitate obtained, the filterate was extracted with cloroform (3x50ml). The chloroform extract was dried over anhydrous sodium sulphate for about three hours and then subjected to removal of solvent by distillation. This yielded a crude orange solid which was combined with the yellow precipitate above. The total mass was then recrystallized from methanol to yield fluffy bright yellow crystals of IX; yield 0.70g (59.5%), m.p. 204-205°. Found: C,64.85; H,3.58; N,14.85%. $C_{15}H_9N_3O_3$ requires C,64.51; H,3.22; N,15.05%. The reaction was also carried out under neutral conditions i.e. without addition of sodium hydroxide solution. However, under these conditions, only 21.3% of IX could be isolated after the extended reaction time of three hours.

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