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A FACILE SYNTHETIC APPROACH TO THE INDENO[1,2-b]PYRROLE SYSTEM BY CYCLOADDITION OF ENAMINES TO NINHYDRIN

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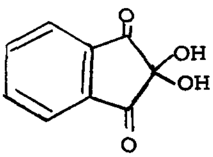
Our interest in the chemistry of ninhydrin hydrate (1), as a modifying agent for nucleic acids[1] and our subsequent studies with aromatic amines[2] and 1, prompted an investigation of the reaction of this reagent with certain enamine systems. Though amino acids and other amines have been extensively studied with respect to their reactions with 1, relatively little is known of the reaction of enamines with this reagent[3]. The Nenitzescu reaction is well documented[4]; however, the reaction of enamines with vicinal polyketones[5] such as 1, does not appear to have been explored. We now report that ninhydrin (1), when allowed to react with enamines such as methyl 3-aminocrotonate, 3-aminocrotononitrile, and 2-aminopentene-4-one, yields stable 1:1-adducts which are assigned structures of the indeno[1,2-b]pyrrole system 2. These structures are assigned on the basis of analytical data[6], and spectral evidence. Thus the pmr spectra of these adducts lacked a vinylic proton signal and showed three exchangeable proton signals due to NH and OH. In addition, compounds 2a and 2c exhibited the molecular ions in their mass spectra (70 eV), unlike the uncyclized carbinolamines reported earlier[2]. The ultraviolet spectra also indicated a 1-indanone chromophore[7], consistent with the cyclized structures.



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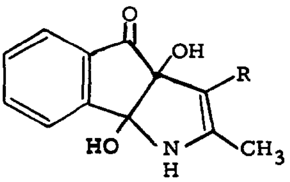
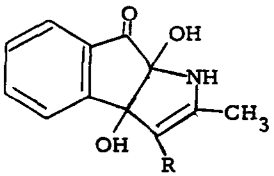


2 a, R= $COOCH_3$
b, R= CN
c, R= $COCH_3$



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The indeno[1,2-b]pyrrole system has been of interest in connection with the search for potential oral hypoglycemic agents[8]. This reaction affords an entry in high yield into the system, which previously required more elaborate procedures. Further, the facile cycloaddition of enamines to ninhydrin should give rise to the heterocyclic ring system which can in principle be transformed into a number of derivatives for purposes of biological evaluation

In a typical reaction, methyl 3-aminocrotonate (2.3 g, 20 mmol) was dissolved in warm water (75 ml); to this solution was added ninhydrin (3.6 g, 20 mmol) in water (55 ml). The mixture was stirred for 1 hr at room temperature. Filtration gave yellow crystals of 2a, mp 198-201° (dec) in 82% yield. Recrystallization from aqueous methanol gave mp 201-202° (dec); ir (KBr) 3389 cm^{-1} (OH), 3215 (NH), 1718 (C=0); uv max (methanol) 245 nm (ϵ 15,700), 275 (22,300); pmr (DMSO-d_6) δ 8.35 (s, 1H, NH), 7.95-7.66 (m, 4H, indanone H), 6.43 (broad s, 1H, OH), 5.50 (broad s, 1H, OH), 3.62 (s, 3H, $COOCH_3$), 2.16 (s, 3H, vinylic CH_3); upon addition of D_2O the signals at 8.35, 6.43, and 5.50 disappeared; mass spectrum m/e 275 (M^+). The other compounds were prepared and characterized similarly; thus 2b mp 215-217° (dec) and 2c mp 210-215° (dec) were obtained in 74 and 71% yield respectively.

The adducts 2 were cleaved by reaction with a ten-fold molar excess of sodium metaperiodate in aqueous solution, to give phthalimide in 35-40% yield. This result excludes the plausible alternative structures 3.

Further studies are in progress to determine the scope and limitations of these cyclization reactions involving vicinal triketone systems[9] and enamines.

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