BENZINDOLS

I. Synthesis of 1-Benzyl-4, 9-diketo-4, 9-dihydrobenzo[f]indole.

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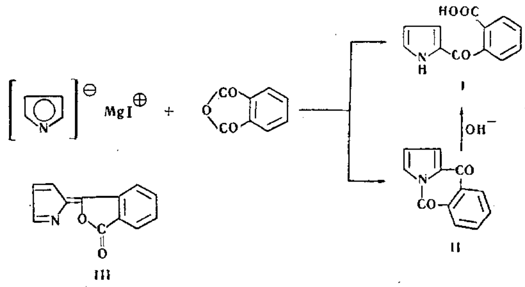
By means of the Grignard reaction between pyrrolmagnesium iodide and phthalic anhydride in anisole, o-(pyrroyl-2)benzoic acid was formed which, after benzylation at the nitrogen atom by the action of phosphorous pentoxide, was converted into 1-benzyl-4, 9-diketo-4, 9-dihydrobenzo[f]indole.

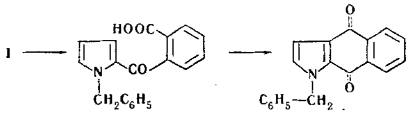
In order to synthesize derivatives of benzo[f]indole, a chemical difficult to obtain, we selected o-(pyrroyl-2)benzoic acid as the original substance. A small yield of the latter had previously been obtained by the interaction between pyrrole and phthalic anhydride in acetic acid at 180° C [1]. It appeared more convenient to use the Grignard reaction with the anhydride of phthalic acid in anisole for this step.



As distinct from indole [2] this reaction does not proceed in a well-defined manner and leads to the formation of two compounds, o-(pyrroyl-2)benzoic acid (I) and its cyclic lactam (II). The structure of the latter was confirmed by the presence of bands at 1715 and 1665 cm^{-1} in the IR spectrum corresponding to the oscillations of the amide [3] and ketone groups and also by the absence of absorption in the region of oscillations of N—H bonds. On the basis of these data one should reject the structure ascribed to this compound of the phthalide of pyrrolenine (III) [1, 4], as an absorption band at 1760–1740 cm^{-1} should have appeared in the IR spectrum characteristic for the carbonyl group of the conjugated anhydride. The IR spectrum of o-(pyrroyl-2)benzoic acid (I) has characteristic absorption bands of the C=O (1630–1695 cm^{-1}), COOH (1720 cm^{-1}), and NH (3445 cm^{-1}) groups. The UV spectra of both compounds markedly from each other (see figure 1). On heating, the keto acid is readily converted into the lactam, which in turn during alkaline hydrolysis gives rise to the keto acid.

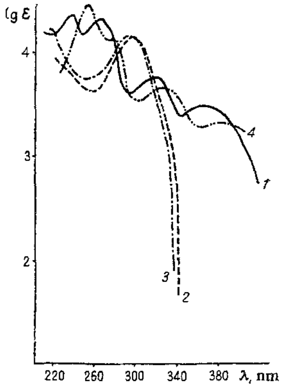
An attempt was then made to reduce the carbonyl group of the acid of compound I. Under the conditions of the Clemmensen reaction in addition to the reduction of the keto group the pyrrole ring is apparently reduced [5, 6], as a result of which a strong resinification is observed. Under the conditions of the Kizhner reaction [7] a stable phthalazone is formed which does not decompose on prolonged boiling with alkali. On reduction with sodium borohydride in methanol the original keto acid is mainly liberated from the reaction. On the basis of the chromatographic analysis on a thin layer of aluminum oxide one might suggest that o-(pyrryl-2)methyl benzoic acid is formed on reduction of the keto acid "by hydrogen at the moment of evolution" on leaching Rainey alloy with a 10% solution of sodium hydroxide. It was found that the products of the reduction in all cases contain a substance with an R_f value of 0.62 (in a system NH_4OH–i-C_3H_7OH–H_2O, 3 : 16 : 1) giving a characteristic blue-violet coloration with Erlich's reagent, although it was not possible to isolate the free reduced acid or its salts.

As the keto acid of I with a free atom of nitrogen in acid medium is readily converted into lactam II, benzylation of the compound was conducted by the action of benzyl chloride in a concentrated solution of potassium hydroxide.



IV V

In the IR spectrum of o-(1-benzylpyrroyl-2)benzoic acid, isolated with a yield of 75%, absorption bands of the carbonyl (1650 cm^{-1}) and carboxyl (1696 cm^{-1}) groups are present.



UV spectra in ethanol: 1) lactam of o-(pyrroyl-2)benzoic acid; 2) o-(pyrroyl-2)benzoic acid; 3) o-(1-benzylpyrroyl-2)benzoic acid; 4) 1-benzyl-4, 9-diketo-4, 9-dihydrobenzo[f]indole.

In order to convert this compound into the derivative of 5, 6-benzidole we conducted cyclization [8, 9] under the action of polyphosphoric acid and phosphorous pentoxide in xylol. In the first case a strong resinification was found. When phosphoric anhydride was used there was also marked resinification, but it was possible to isolate the quinone of compound V with a yield of 25%. The structure of this compound was confirmed by the presence of an absorption band in the IR spectrum characteristic for the quinoid structure (1660 cm^{-1}) and a band at 3125 cm^{-1} apparently caused by the valency oscillations of the CH group in the linear aromatic system and also by the nature of curve in the UV spectrum (figure).

EXPERIMENTAL

o-(Pyrroyl-2)benzoic acid (I). A 45 g (0.28 mole) quantity of ethyl iodide was added dropwise over the course of 45 min to 6.9 g (0.28 g-at.) of magnesium filings in 70 ml of dry anisole. The mixture was heated at 60–70° C for 45–60 min during mild agitation until the magnesium had completely dissolved. It was then cooled with ice and, during intensive mixing, 19.6 g (0.28 mole) of pyrrole in 70 ml of anisole were added dropwise over the course of 30 min. The mixture was stirred for 15 min at room temperature and then at 50–60° C until the evolution of ethane bubbles had completely ceased (15 min). A hot solution of 43.4 g (0.29 mole) of phthalic anhydride in 140 ml anisole was poured rapidly (within 2–3 min) on to the pyrrylmagnesium idodide cooled to room temperature. During this procedure the mixture warmed up markedly (up to 100–110° C) and a light brown complex was formed which was converted into a powder on vigorous stirring. In order to complete the reaction, the mixture was heated for 60–90 min on a boiling water bath and then it was cooled and decomposed with acetic acid (60 ml of acetic acid in 150 ml of water). The liquid layer was decanted from the resin-like precipitate into a separating funnel. On grinding in water the precipitate hardens, and it was removed by filtration, washed with water, and dried. The resulting blackish-brown powder (10 g) during sublimation (240° C, approximately 50 mm) gives rise to the lactam of compound II in the form of yellow needles (3 g). Mp 240–241° C (from acetone). R_f 0.86 (Al_2O_3, isopropyl alcohol–ammonia–water, 16 : 3 : 1). UV spectrum: λ_{max} 238, 264, 318, 370 nm; log ε 4.35, 4.31, 3.75, 3.48 (in ethanol). IR spectrum, cm^{-1}: 1665 (C=O); 1715 (CONH) (in vaseline oil). Found, %: C 73.03; H 3.55; N 7.08. Calculated for $C_{12}H_7NO_2$, %: C 73.09; H 3.58; N 7.1.

The anisole layer was shaken with a 10% solution of NaOH. The precipitate in the form of fine crystals was removed by filtration, and it was dissolved in water on heating, and on cooling the keto acid was precipitated by the addition of conc HCl. The alkaline filtrate was also acidified with conc HCl. The precipitated o-(pyrroyl-2)benzoic acid (I) was removed by filtration, washed with water and again precipitated from dilute alkali. The total yield of keto acid was 18.8 g (30%). Mp 184–185° C (from aqueous alcohol, 1 : 1). R_f = 0.30 (Al_2O_3, isopropyl alcohol–ammonia–water, 16 : 3 : 1). UV spectrum: λ_{max} 296 nm; log ε 4.14 (in ethanol). IR spectrum cm^{-1}: 1630–1695 (C=O); 1720 (COOH); 3445 (NH) (in vaseline oil). Found, %: C 67.06; H 4.21; N 6.50. Calculated for $C_{12}H_9NO_3$, %: C 67.00; H 4.21; N 6.51.

o-(1-Benzylpyrroyl-2)benzoic acid (IV). A mixture of 2.15 g (0.01 mole) of compound I, 40 ml of a 35% solution of potassium hydroxide, and 6.5 g (0.05 mole) of benzyl chloride was boiled with mixing for 6 hr. The upper layer was separated and acidified with HCl until it gave an acid reaction with Congo red, and it was then extracted with ether. The ethereal solution was dried with anhydrous sodium sulfate and the ether was evaporated under vacuum. On cooling, the acid of compound IV crystallized from the oil-like residue, and it was removed by filtration and washed with benzene. Yield 2.45 g (75%), mp 139–140° C (from alcohol or benzene). R_f, 0.53 (Al_2O_3, isopropyl alcohol–ammonia–water, 16 : 3 : 1). UV spectrum: λ_{max}, 296 nm; log ε, 4.14 (in ethanol) IR spectrum, cm^{-1}: 1650 (C=O), 1695 (COOH) (in vaseline oil). Found, %: C 74.90; H 4.93; N 4.85. Calculated for $C_{19}H_5NO_3$, %: C 74.74; H 4.95; N 4.59.

1-Benzyl-4, 9-diketo-4, 9-dihydrobenzo[f]indole (V). A 10 g quantity of phosphorous pentoxide was introduced in small portions over 30 min into a solution of 1.6 g of the acid of compound IV in 200 ml of hot o-xylol. The mixture was boiled for 90 min. The resinlike reaction product was separated and washed with xylol. The xylol was evaporated under vacuum. Yield of compound V 0.3 g; mp 178–179° C (from alcohol). R_f, 0.64 (Al_2O_3, benzene). UV spectrum: λ_{max} 254, 236, 382, 388 nm; log ε, 4.45, 3.68, 3.34 (in ethanol). IR spectrum, cm^{-1}: 1660 (quinone), 3125 (C—H) (in vaseline oil). Found, %: C 79.22; H 4.73; N 4.88. Calculated for $C_{19}H_{13}NO_2$, %: C 79.42; H 4.62; N 4.95.

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