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REACTION OF ARALKYL KETONE PHENYLHYDRAZONES WITH CARBON MONOXIDE; THERMAL INDOLIZATION OF ARALKYL KETONE PHENYLHYDRAZONES

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This note summarizes the principal results obtained when aralkyl ketone phenylhydrazones were caused to react with carbon monoxide using dicobalt octacarbonyl as a catalyst. In earlier work (1, 2) it was shown that aromatic ketone and aldehyde phenylhydrazones containing a C=N group which was conjugated to an aromatic ring cyclized with carbon monoxide to yield N-substituted phthalimidines. Under similar conditions, aralkyl ketone phenylhydrazones might be expected to undergo ring closure to afford heterocyclic substances having six or more members.

Reaction of desoxybenzoin phenylhydrazone with carbon monoxide at 3 500 p.s.i. and a temperature of 235° for 3 h in the presence of preformed dicobalt octacarbonyl afforded mainly 2,3-diphenylindole (I), 3-benzylphthalimidine-N-carboxyanilide (II), 3-benzyl-2-phenylphthalimidine (III), and *sym*-diphenylurea (IV) in 20, 22, 11, and 27% yields, respectively. Separation of these components was achieved by thin-layer chromatography on silica gel G using benzene–methanol (95:5 v:v) as developer or by alumina column chromatography.

I II III IV

Compounds I and IV were identified by direct comparison with authentic samples of 2,3-diphenylindole and *sym*-diphenylurea, respectively. Reaction of 3-benzylphthalimidine with phenylisocyanate afforded an authentic sample of 3-benzylphthalimidine-N-carboxyanilide which was identical (melting point and infrared spectrum) with compound II. Condensation of benzylidene phthalide with aniline afforded 3-benzylidene-2-phenylphthalimidine. Reduction of the latter substance with 1 mole of hydrogen over platinum oxide as catalyst yielded authentic 3-benzyl-2-phenylphthalimidine having an infrared spectrum which was identical with that of substance III.

Although the high-pressure cyclization reaction of desoxybenzoin phenylhydrazone with carbon monoxide demonstrates the preferential formation of the five-membered ring over the six-membered ring, it did not establish if a six-membered ring could be formed. To ascertain if a six-membered ring could be formed, 1,3-diphenyl-2-propanone phenylhydrazone was treated with carbon monoxide in the presence of dicobalt octacarbonyl. In the latter case no six-membered ring was formed. Interestingly, 2,3-diphenylindole accompanied the product that was obtained from desoxybenzoin phenylhydrazone, and 2-benzyl-3-phenylindole was the major product (65% yield) of the reaction of 1,3-diphenyl-2-propanone phenylhydrazone with carbon monoxide in the presence of dicobalt octacarbonyl.

Because the indoles were formed from the aralkyl ketone phenylhydrazones when the reaction was carried out in the presence of dicobalt octacarbonyl, it was felt that cobalt hydrocarbonyl (which would be formed from the dicobalt octacarbonyl) might be essential for the conversion of the hydrazones into the indoles. This speculation was proved to be incorrect by showing that the same conversion into indoles in higher yield (about 80%) occurred without the presence of the catalyst. A similar thermal indolization of hydrazones has recently been reported by other workers (3).

In the reaction of 2-ethoxy-1-naphthaldehyde phenylhydrazone with carbon monoxide, ring closure to the 8-position was expected, since the 2-position was blocked. However, no cyclization occurred. From these results, as well as those of other workers (4, 5), evidently only five-membered heterocycles can be formed from aromatic compounds containing the C=N group.

EXPERIMENTAL

Melting points are corrected. The alumina used for column chromatography was obtained from British Drug Houses. All molecular weights were determined by mass spectrometry by Mr. F. Bloss of this department on an Atlas CH4 spectrometer. Microanalysis was done in this department.

The high-pressure equipment and general procedure have been described previously (1, 2).

Reaction of Desoxybenzoin Phenylhydrazone with Carbon Monoxide to Yield 2,3-Diphenylindole (I), 3-Benzylphthalimidine-N-carboxyanilide (II), and 3-Benzyl-2-phenylphthalimidine (III)

Desoxybenzoin phenylhydrazone (11 g) was allowed to react with carbon monoxide at 235° and a pressure of 3 500 p.s.i. for 3 h in the presence of dicobalt octacarbonyl (2 g) as described previously (1). After removal of the catalyst, the benzene was evaporated under reduced pressure at 30°. Evaporation of the residual oil under reduced pressure at about 100° afforded aniline (0.5 g, 13%). Crystallization of the residual oil in 50 ml of hot benzene yielded 1.2 g (27%) of *sym*-diphenylurea which was recrystallized from chloroform; m.p. 251–252°; the mixed melting point with an authentic sample of *sym*-diphenylurea was 251–252°.

A 25 ml aliquot of the filtrate was chromatographed on alumina (120 × 71 mm diameter). Benzene (500 ml) eluted 0.23 g of an oil which possessed no carbonyl group.

Substance I (2,3-diphenylindole) was then eluted with 400 ml of benzene; yield 1.1 g (20%). Recrystallization of compound I from cyclohexane gave pure material; m.p. 123–124°; the mixed melting point with an authentic sample of 2,3-diphenylindole (6) was 123–124°. The infrared spectra of both compounds were identical.

Compound II (3-benzylphthalimidine-N-carboxyanilide) was then eluted with 3 000 ml of a 4:1 mixture of benzene–chloroform; yield 1.2 g (22%). Recrystallization of compound II from cyclohexane afforded the pure carboxyanilide; m.p. 146–147°; the mixed melting point with an authentic sample prepared by steps described below was 146–147°. The infrared spectra of both compounds were identical.

Elution of the column with a further 1 500 ml of the benzene–chloroform mixture gave 1.2 g of a mixture of compounds II and III. This mixture was separated by rechromatography on a new alumina column using benzene–ethanol (99.5:0.5) as developer. The yields reported for II and III include the material obtained from the rechromatography of the mixture.

Fraction III (3-benzyl-2-phenylphthalimidine) was then eluted with 1 600 ml of benzene–ethanol (98:2 v:v); yield 1.2 g (11%). Compound III was recrystallized from cyclohexane; m.p. 124–125°; the mixed melting point with a sample prepared by unambiguous steps as described below was 124–125°. The infrared spectra of both compounds were identical.

Thin-layer chromatography of the original product mixture on silica gel G using benzene–methanol (95:5) as developer showed the presence of trace quantities of at least three additional components.

Thermal Indolization of Desoxybenzoin Phenylhydrazone and of 1,3-Diphenylpropanone Phenylhydrazone

Desoxybenzoin phenylhydrazone dissolved in benzene was heated in an autoclave at 235° for 3 h in the absence of catalyst. 2,3-Diphenylindole was obtained in 80% yield. Similarly, 1,3-diphenylpropanone phenylhydrazone was converted thermally in 75% yield into 2-benzyl-3-phenylindole.

Reaction of 2-Ethoxy-1-naphthaldehyde Phenylhydrazone with Carbon Monoxide

2-Ethoxy-1-naphthaldehyde phenylhydrazone (7 g) was allowed to react with 3 500 p.s.i. of carbon monoxide in the presence of dicobalt octacarbonyl (1 g) in 35 ml of benzene at a temperature of 235° for 3 h. The product (freed of catalyst) was chromatographed on alumina using benzene–chloroform (8:1 v:v) as developer, and was shown to contain no cyclic carbonyl group.

Reaction of 1,3-Diphenyl-2-propanone Phenylhydrazone with Carbon Monoxide

1,3-Diphenyl-2-propanone phenylhydrazone was allowed to react with high purity carbon monoxide in the presence of dicobalt octacarbonyl, and the product worked up as described previously. The main component, 2-benzyl-3-phenylindole, m.p. 100–101°, was obtained in 65% yield. The mixed melting point of the main component and an authentic sample of 2-benzyl-3-phenylindole (7) was 100–101°. In addition, *sym*-diphenylurea was produced in about 20% yield. The remaining product, which consisted of traces of different compounds, contained no cyclic carbonyl group.

Synthesis of Authentic 3-Benzylphthalimidine-N-carboxyanilide

3-Benzylphthalimidine (8) was allowed to react with phenylisocyanate as described previously (1) to afford 3-benzylphthalimidine-N-carboxyanilide; m.p. 146–147°. The infrared spectrum of this substance in a KBr pellet was identical with that of compound II and showed strong carbonyl bands at 1 705 and 1 670 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: N, 8.18; mol. wt. 342. Found: N, 8.44; mol. wt. (by mass spectrum) 342.

Synthesis of 3-Benzyl-2-phenylphthalimidine

(a) 3-Benzylidene-2-phenylphthalimidine

Benzylidene phthalide (3 g) (9), aniline (10 g), and ethyl alcohol (15 ml) were refluxed for 5 h. After the alcohol was evaporated, the remaining oil was dissolved in hot acetic acid. The solid which precipitated from the mixture was recrystallized from ethanol to afford 3-benzylidene-2-phenylphthalimidine; m.p. 200–201°.

Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.25; H, 5.02; N, 4.68. Found: C, 84.10; H, 4.91; N, 4.84.

(b) 3-Benzyl-2-phenylphthalimidine

3-Benzylidene-2-phenylphthalimidine (0.1 g) dissolved in 10 ml of chloroform–ethanol (1:1) was hydrogenated over reduced platinum oxide until 1 mole of hydrogen per mole of substrate was absorbed. After the catalyst was removed by filtration, the solvent was evaporated and the product recrystallized from cyclohexane; m.p. 124–125°. Reduction of 3-benzylidene-2-phenylphthalimidine in chloroform – acetic acid with the same catalyst gave a compound that was contaminated with trace quantities of a material having one aromatic ring which was reduced, as shown by its mass spectrum. The infrared spectrum of 3-benzyl-2-phenylphthalimidine showed a strong carbonyl peak at 1 680 cm^{-1}.

Anal. Calcd. for $C_{21}H_{17}NO$: N, 4.68; mol. wt. 299. Found: N, 4.65; mol. wt. (by mass spectrum) 299.

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