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Seishi Takagi, Atsushi Sugii, and Katsunosuke Machida : Synthesis of Indolyl Aryl 1,2-Diketones.

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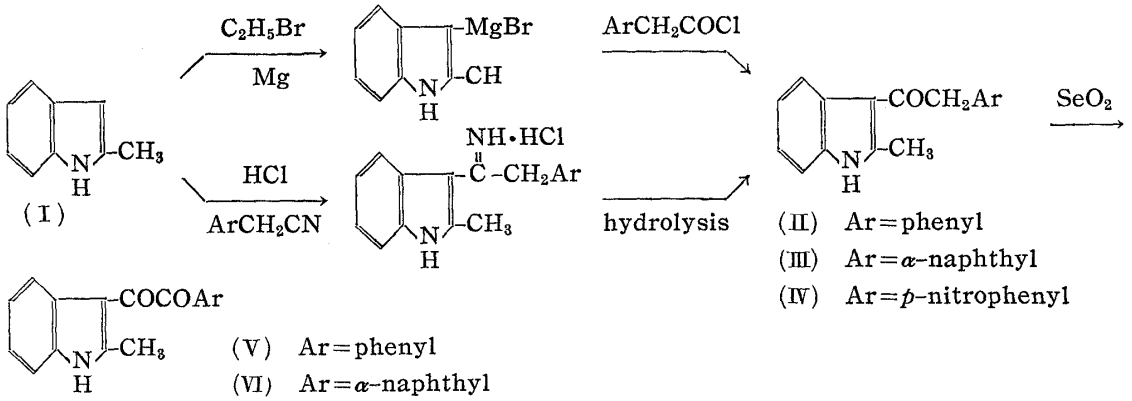
Various kinds of aromatic and heterocyclic 1,2-diketones have been synthesized for the purpose of investigating pharmacological activitiy of the substituted glycolic acid esters derived from the corresponding 1,2-diketones by benzilic acid rearrangement.

There have been no report regarding the synthesis of indolyl aryl 1,2-diketones, which may be obtained by the arylacetylation of indoles and successively the oxidation of the methylene group between aryl and carbonyl groups. In this point of view, we attempted to synthesize some indolyl aryl 1,2-diketones (indolylarylglyoxals). Both the Grignard[1] and Hoesch[2] reactions have been used to introduce an acyl group into 3-position of indoles having no substituent at 1-position. Because the former method requires less time than the latter, we began with this method.



In an ethereal solution of ethylmagnesium bromide, 2-methylindole (I), prepared from acetone and phenylhydrazine by Fischer's method,[3] was treated with arylacetyl chlorides under stirring and ice cooling, then the reaction mixture was treated with aqueous $NaHCO_3$. 2-Methyl-3-phenylacetylindole (II) and 2-methyl-3-α-naphthylacetylindole (III) were obtained in this manner, but a small amount of 2-methyl-3-*p*-nitrophenylacetylindole (IV) was formed because of large extent of resinification in the course of the reaction.

By the Hoesch reaction, however, (II) and (IV) were obtained in better yields. Seka reported that (II) had been obtained in 80% yield by this method.[2] Dried HCl gas was passed into an ethereal solution of (I) and benzyl cyanide. The ketimine hydrochloride formed was decomposed to (II) by boiling with aqueous ammonia. In the case of (IV), *p*-nitrobenzyl cyanide was suspended in the ethereal solution of (I) and stirring was prolonged. The ketimine hydrochloride was decomposed by boiling only with water.

The active methylene group of 2-methyl-3-arylacetylindole was oxidized with selenium dioxide, which had been used in the oxidation of desoxybenzoins to benzils.[4]

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1) A.H. Salway : J. Chem. Soc., **103**, 355(1913).
2) R. Seka : Ber., **56**, 2058(1923).
3) E. Fischer : Ber., **19**, 1563(1886).
4) E.L. Bockstahler, D.L. Wright : J. Am. Chem. Soc., **71**, 3760(1949).

In the oxidation of (IV), the reaction mixture rapidly resinified and the product could not be separated.

In ethanolic alkali, (V) underwent the benzilic acid rearrangement neither by standing over night at room temperature nor by refluxing on a water bath for two or three hours. In both attempts to carry out the rearrangement, a large amount of (V) was recovered from the reaction mixture. Further researches are necessary for suitable conditions of the rearrangement.

We are indebted to the members of the Microanalytical Laboratory of this Institute for carrying out microanalyses.

Experimental

2-Methyl-3-phenylacetylindole (II)—(Grignard method) To a Grignard reagent (Mg 3 g., C_2H_5Br 13 g., and Et_2O 40 cc.) a solution of (I) (15 g.) in Et_2O (20 cc.) was added dropwise under water cooling, and stirring was continued for 1 hr. at room temperature. Then a solution of phenylacetyl chloride (17 g.) in Et_2O (15 cc.) was added dropwise under ice cooling, the reaction mixture became scarlet and viscous mass was formed. The mixture was allowed to stand for 1 hr., the Et_2O layer was removed, and the residue was treated with saturated aq. $NaHCO_3$, left to stand over night, and filtered. Recrystallization from EtOH yielded 8.9 g. of white crystals, m.p. 198~199°, undepressed on admixture with (II) obtained by the Hoesch method.[2] *Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06. Found : C, 81.42; H, 6.34.

2-Methyl-3-α-naphthylacetylindole (III)—(Grignard method) Mg (1.25 g.), C_2H_5Br (5.5 g.), (I) (6.5 g.), and α-naphthylacetyl chloride (10 g.) were treated similarly. Recrystallization from EtOH yielded 4 g. of white crystals, m.p. 221°(decomp.).[3] *Anal.* Calcd. for $C_{21}H_{17}NO$: C, 84.25; H, 5.72. Found : C, 83.77; H, 5.93.

2-Methyl-3-*p*-nitrophenylacetylindole (IV)—(Grignard method) Mg (2.2 g.), C_2H_5Br (9 g.), (I) (12 g.), and a suspension of *p*-nitrophenylacetyl chloride (16 g.) in Et_2O (20 cc.) were treated similarly. The product did not crystallize after standing over night with saturated aq. $NaHCO_3$. Then water layer was removed, the pitchy mixture was digested with EtOH and filtered, the filtrate was concentrated and the pale yellow crystals formed were repeatedly recrystallized from EtOH. The yield was 0.5 g., m.p. 212°. *Anal.* Calcd. for $C_{17}H_{14}O_3N_2$: C, 69.38; H, 4.79. Found : C, 69.32; H, 5.09.

(Hoesch method) *p*-Nitrobenzyl cyanide (11 g.) was suspended in a solution of (I) (4 g.) in Et_2O (20 cc.). With stirring and ice cooling, dried HCl gas was passed into the suspension for 7 hrs. The reactant was placed in an air-tight container and was left to stand 3 days in an ice box. The amorphous mass was separated from the Et_2O layer, boiled succesively with water for 3 hrs. and with EtOH for 1 hr. The crystalline residue was recrystallized from EtOH. The yield was 3.2 g., m.p. 212°, undepressed on admixture with (IV) obtained by the former method. *Anal.* Calcd for $C_{17}H_{14}O_3N_2$: C, 69.38; H, 4.79. Found : C, 69.35; H, 4.99.

2-Methyl-3-indolylphenylglyoxal (V)—A suspension of (II) (2.4 g.) and SeO_2 (2.1 g.) in dioxane (5 cc.) was refluxed for 4 hrs. in an oil bath. The color of reaction mixture rapidly changed from white to reddish brown. The solvent was removed under reduced pressure, the residue was extracted with benzene, and passed through an alumina column (30×1.2 cm., 30 g.). The yellow crystals formed from concentrated effluent were recrystallized from benzene. The yield was 1.5 g., m.p. 176~177°. *Anal.* Calcd. for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98. Found : C, 77.61; H, 5.20.

2-Methyl-3-indolyl-α-naphthylglyoxal (VI)—(III) (3.0 g.), SeO_2 (2.1 g.), and dioxane (20 cc.) were treated similarly. Recrystallization from EtOH-benzene (1:10) yielded 1.0 g. of pale yellow crystals, m.p. 236°(decomp.). *Anal.* Calcd. for $C_{21}H_{15}O_2N$: C, 80.49; H, 4.82. Found : C, 80.41; H, 4.90.

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