METHYL γ-PHENYLACETATE IN THE FISCHER INDOLE SYNTHESIS

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Nitrogen-substituted methyl γ-phenyl-β-hydrazinocrotonates form methyl 3-phenyl-2-indolylacetates or methyl 2-benzylindole-3-carboxylates in acid media. The latter react with polyphosphoric acid to give benzo[b]carbazole derivatives, from which the corresponding 6,11-dioxobenzo[b]carbazoles are obtained by oxidation.

Fischer indolyzation of the product of the reaction of γ-phenylacetoacetic ester with N-methyl-N-phenylhydrazine leads to ethyl 3-phenyl-2-indolylacetate, but the structure of the latter has not been proved [1]. In addition, methyl 2-benzylindole-3-carboxylates [2] are obtained by the condensation of methyl γ-phenyl-β-aminocrotonates with p-benzoquinone under the conditions of the Nenitzescu reaction, which can be considered to be a process similar to the formation of indoles via the Fischer reaction. We have investigated the cyclization of nitrogen-substituted methyl γ-phenyl-β-hydrazinocrotonates (I-III).* As in the IR spectra of methyl γ-phenyl-β-(N-methylamino)crotonate, absorption bands at 3250-3260 cm^{-1} (ν_{NH}), 1660 cm^{-1} ($\nu_{C=O}$), and 790 cm^{-1} (γ-$R_1R_2C=CHR_3$) are present in the IR spectra of I and II, obtained by the reaction of methyl γ-phenylacetoacetate with asymmetrical methylphenyl- and methyl(p-anisyl)hydrazines. Singlet signals at 9.47 (NH) and 4.49 ppm (α-methylidyne group) are observed in the PMR spectrum of I. The presence of a methylphenylhydrazine grouping in I leads to magnetic nonequivalence of the protons of the γ-methylene group. The signals of the latter are represented in the spectrum in the form of two doublets at 3.56 and 3.34 ppm, respectively, with a spin–spin coupling constant of 15 Hz. The position of the signals of the protons in the PMR spectrum is a confirmation of the fact that I-III have hydrazinocrotonic ester structures. The chemical shift of the CH_2 group (~3.4 ppm) is due to the effect of the adjacent aromatic ring. If the latter were absent, i.e., in isomeric structure A, the corresponding shift would be 2.2-2.4 ppm. In addition, the position of the signal of the methylidyne proton (~4.5 ppm) corresponds to the absence of an adjacent phenyl group, which would shift it considerably to the weak-field region.

According to the mechanism adopted for the Fischer reaction [3,4], I-III should be converted to methyl 2-benzylindole-3-carboxylates. We have established that, depending on the conditions, the reaction gives different indole derivatives. Thus methyl 3-phenyl-2-indolylacetates (IV-VI) are obtained in 77-92% yield in the reaction of sulfuric acid in methanol with I-III at room temperature. Under these conditions, esters of 2-benzylindole-3-carboxylic acid are apparently formed in low yields. One of them – VII – which we have previously obtained [2], could be isolated from the mother liquor in 2% yield. The IR spectra of IV-VI contain a band of the stretching vibrations of a carbonyl group at 1740 cm^{-1}, which corresponds to the absorption of the carbonyl group of indolylacetic acid esters [5]. Hydrolysis of IV and subsequent decarboxylation of the resulting acid (VIII) gives 1,2-dimethyl-3-phenylindole (IX), which is identical to a sample obtained by methylation of 2-methyl-3-phenylindole [6]. Signals of the protons of two CH_3 groups at 2.2 and 3.3 ppm are observed in the PMR spectrum of IX. The formation of 3-phenylindole derivatives instead of 2-benzylindole derivatives may apparently be explained by the conversion of I-III to isomeric compounds (A) during the reaction.

*Compound III was introduced into the cyclization reaction without isolation and additional purification.

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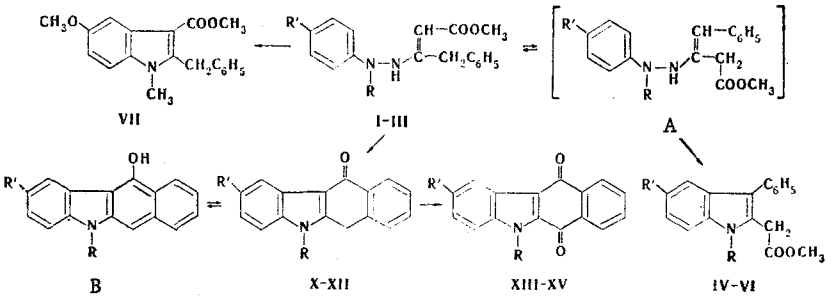
It is known that polyphosphoric acid (PPA) brings about specific cyclization of phenylacetone phenylhydrazone [6,7], which leads not only to 2-methyl-3-phenylindole but also to 2-benzylindole. We have found that 6,11-dihydro-11-oxobenzo[b]carbazole derivatives (X-XII) are formed in the reaction of PPA with I-III. The reaction probably proceeds through a step involving formation of methyl 2-benzylindole-3-carboxylates with subsequent intramolecular cyclization. We also obtained XI from the reaction of 1-methyl-2-benzyl-5-methoxyindole-3-carboxylic acid [2] with PPA. A signal from the protons of a methylene group is observed in the PMR spectrum of a chloroform solution of XI at 3.50 ppm, while OH group absorption is absent above 3000 cm^{-1} in the IR spectrum under these conditions, and an intense band is observed at 1635 cm^{-1} ($\nu_{C=O}$). These data constitute proof that benzocarbazoles X-XII exist in the oxo form. At the same time, the IR spectrum of a suspension of XI in mineral oil contains an absorption band at 3250 cm^{-1} (ν_{OH}). In this connection, there is a basis for supposing that a phenomenon of the anthrone–anthranol tautomerism (XI ⇌ B) type occurs for derivatives X-XII.

In the absence of catalysts, the indolyzation of II at 190-200° proceeds to give chiefly a 2-benzylindole derivative (VII), and the 3-phenylindole derivative (V) is formed in a yield of only 1.8%. The corresponding 6,11-dioxobenzo[b]carbazoles (XIII-XV) are obtained in the oxidation of X-XII with chromic acid.



I, IV, X, XIII R=CH_3; R′=H II, V, XI, XIV R=CH_3; R′=OCH_3
III, VI, XII, XV R=$CH_2C_6H_5$; R′=H

EXPERIMENTAL

The IR spectra of mineral oil suspensions (and of a chloroform solution in the case of XI) of the substances were obtained with a Perkin-Elmer spectrophotometer. The PMR spectra of carbon tetrachloride solutions (I and IX) and chloroform solutions (XI) were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz on the δ scale relative to tetramethylsilane or hexamethyldisiloxane.

Methyl γ-Phenyl-β-(N-methyl-N-phenylhydrazino)crotonate (I). An 11.5-g (0.06 mole) sample of methyl γ-phenylacetoacetate and 7.3 g (0.06 mole) of N-methyl-N-phenylhydrazine were mixed, one drop of glacial acetic acid was added, and the mixture was allowed to stand for 2-3 h. Workup gave 17 g (95.5%) of a product with mp 91-92° (from methanol). PMR spectrum, ppm: N–CH_3 (2.66 s*), γ-CH_2 (3.41 q, J = 15 Hz), $COOCH_3$ (3.55 s), α-CH (4.49 s), $2C_6H_5$ (6.80 m, 7.10 s), NH (9.47 s). Found: C 72.9; H 7.0; N 9.4%. $C_{18}H_{20}N_2O_2$. Calculated: C 72.9; H 6.8; N 9.5%.

Methyl γ-Phenyl-β-[N-methyl-N-(p-anisyl)hydrazino]crotonate (II). This compound was obtained in quantitative yield under similar conditions and had mp 114-115° (from methanol). Found: C 69.9; H 6.6; N 8.5%. $C_{19}H_{22}N_2O_3$. Calculated: C 69.9; H 6.8; N 8.6%.

Methyl 1-Methyl-3-phenyl-2-indolylacetate (IV). A solution of 6 ml of concentrated sulfuric acid in 60 ml of methanol was added dropwise with stirring at room temperature to 9.6 g (0.032 mole) of I, and the reaction mass was allowed to stand for 1 h. It was then cooled with ice, and the resulting precipitate was removed by filtration, washed with water, and dried to give 8.3 g (92.2%) of a product with mp 100-101° (from methanol). Found: C 77.5; H 6.2; N 5.0%. $C_{18}H_{17}NO_2$. Calculated: C 77.4; H 6.1; N 5.0%.

Methyl 1-Methyl-3-phenyl-5-methoxy-2-indolylacetate (V) and Methyl 1-Methyl-2-benzyl-5-methoxyindole-3-carboxylate (VII). A. The reaction was carried out under the conditions used in the synthesis of IV to give 77% of V with mp 121-122° (from methanol). Found: C 74.0; H 6.3; N 4.7%. $C_{19}H_{19}NO_3$. Calculated: C 73.8; H 6.2; N 4.5%.

*Abbreviations: s is singlet, q is quartet, and m is multiplet.

The mother liquor after the separation of V was treated with water, and the resulting resinous mass began to crystallize on cooling to give 2.1% of VII with mp 135-136° (from methanol). This product did not depress the melting point of a sample of methyl 1-methyl-2-benzyl-5-methoxyindole-3-carboxylate that we previously obtained in [2].

B. A 6-g sample of II was heated on a Woods metal bath at 190-200° until the evolution of ammonia bubbles ceased (3-5 min). The residue in the flask was cooled and stirred with a small amount of methanol. The resulting crystals were removed by filtration, washed with methanol, and dried to give 2.1 g (37%) of a mixture of V and VII, which, according to gas-liquid chromatography (GLC), * contained 1.83% V and 97.8% VII.

Methyl 1-Benzyl-3-phenyl-2-indolylacetate (VI). A 1.92-g (0.01 mole) sample of methyl γ-phenylacetoacetate and 1.98 g (0.01 mole) of N-benzyl-N-phenylhydrazine were mixed, and 1 drop of glacial acetic acid was added. The methyl γ-phenyl-β-(N-benzyl-N-phenylhydrazino)crotonate (III), which separated as an oil, was dried by azeotropic distillation of the water with benzene. The benzene was removed by distillation, and a solution of 1.2 ml of concentrated sulfuric acid in 12 ml of methanol was added to the residue in the flask. The resulting VI, which separated as an oil, began to crystallize on cooling to give 2.9 g (83%) of a product with mp 99-100° (from methanol). Found: C 81.0; H 6.0; N 3.6%. $C_{24}H_{21}NO_2$. Calculated: C 81.1; H 6.0; N 3.9%.

1-Methyl-3-phenyl-2-indolylacetic Acid (VIII). A 5.6-g (0.02 mole) sample of IV was added to fused potassium hydroxide obtained by heating 11.2 g (0.2 mole) of potassium hydroxide with 2 ml of water to 150°. The melt was stirred at 150-170° for 5-7 min until the evolution of gas bubbles ceased. The melt was then cooled and dissolved in 50 ml of distilled water. The solution was filtered, and the filtrate was acidified with acetic acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 4.9 g (98.4%) of a product with mp 140-141° (from aqueous acetone) (mp 142° [1]). Found: C 77.3; H 5.6; N 5.3%. $C_{17}H_{15}NO_2$. Calculated: C 77.0; H 5.7; N 5.3%.

1,2-Dimethyl-3-phenylindole (IX). A. A 0.6-g (2.5 mmole) sample of VIII was heated on a Woods metal bath at 165-170° in a flask equipped with an air condenser with a Bunsen valve until the evolution of carbon dioxide bubbles ceased. The resulting oily liquid (IX) crystallized on cooling to give 0.5 g (94.3%) of a product with mp 111-112° (from methanol) (mp 111-112.5° [8]). Found: C 87.0; H 6.9; N 6.3%. $C_{16}H_{15}N$. Calculated: C 86.8; H 6.8; N 6.3%.

B. A hot solution of 2 g (0.05 mole) of potassium hydroxide in 1 ml of water was added all at once to a solution of 2 g (0.01 mole) of 2-methyl-3-phenylindole [6] in acetone, and the mixture was stirred for 45 min. Dimethyl sulfate [1.9 ml (0.02 mole)] was then added to the reaction solution in the course of 5 min, and the mixture was stirred at room temperature for 45 min. The mixture was poured into water, and the resulting precipitate was removed by filtration, washed with water, and dried to give 2.1 g (95.5%) of a product with mp 111-112° (from methanol). This product did not depress the melting point of the product obtained by method A.

6,11-Dihydro-5-methyl-11-oxobenzo[b]carbazole (X). A 40-g (0.035 mole) sample of I was added at room temperature to 400 g of polyphosphoric acid [9], and the mixture was stirred at 50-60° for 1 h. The reaction mass was then cooled and poured with stirring over ice. The resulting precipitate was removed by filtration, washed with saturated sodium bicarbonate solution and water, and dried to give 14.5 g (43.4%) of a substance which, after recrystallization from methanol–ethyl acetate (1:1), had mp 189-190.5° (dec.) and R_f 0.62. † Found: C 82.7; H 5.2; N 5.7%. $C_{17}H_{13}NO$. Calculated: C 82.6; H 5.3; N 5.7%.

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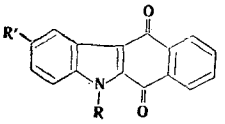
*The composition of the reaction product was studied with a JGC-810 gas-liquid chromatograph. The 0.5-m long column had a cross section of 3 mm. The stationary phase was 1% OV-17 and 1% SE-30 on Chromosorb W. The column temperature was 197°, and the carrier gas (helium) flow rate was ~60 ml/min. Individual samples of V and VII that we had previously obtained were used as references for the identification of the chromatographed peaks. The percentage of V and VII was determined by means of a Chromalog-2 electronic integrator.

† The benzocarbazole derivatives (X-XII) were chromatographed under the same conditions: the adsorbent was Silufol UV-254, the elution was accomplished with benzene–methanol (9:1), and the spots were developed with iodine vapors.

TABLE 1. 6,11-Dioxobenzo[b]carbazole Derivatives



Comp.	R	R′	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
XIII	CH_3	H	211—212	$C_{17}H_{11}NO_2$	78,1	4,3	5,4	78,2	4,2	5,4	50
XIV	CH_3	OCH_3	257,5—258,5	$C_{18}H_{13}NO_3$	74,2	4,6	4,9	74,2	4,5	4,8	62
XV	$CH_2C_6H_5$	H	178,5—179,5	$C_{23}H_{15}NO_2$	81,8	4,4	4,1	81,9	4,5	4,2	35,7

*From glacial acetic acid.

6,11-Dihydro-5-methyl-2-methoxy-11-oxobenzo[b]carbazole (XI). A. Compound XI was obtained from II under the conditions of the synthesis of X, during which the reaction mixture was stirred at room temperature for 2 h. The yield of product with mp 169-171° [from ethyl acetate–glacial acetic acid (3:1), in a sealed capillary] and R_f 0.48 was 44%. Found: C 78.0; H 5.7; N 5.1%. $C_{18}H_{15}NO_2$. Calculated: C 78.0; H 5.5; N 5.1%.

B. A 1.5-g (5 mmole) sample of 1-methyl-2-benzyl-5-methoxyindole-3-carboxylic acid [2] was added to 80 g of polyphosphoric acid, and the mixture was stirred at room temperature for 5 h and allowed to stand overnight. It was then cooled and diluted with water, and the resulting precipitate was removed by filtration, washed with water, and dried. It was then dissolved by heating in the minimum amount of dioxane, a saturated sodium bicarbonate solution was added, and the mixture was heated almost to the boiling point. It was then cooled and diluted with three to four volumes of water, and the precipitate was removed by filtration, washed with water, and dried to give 1.3 g (95%) of a product with mp 169-171° [in a sealed capillary, from ethyl acetate–glacial acetic acid (3:1)] and R_f 0.48. Found: C 77.9; H 5.7; N 5.1%. $C_{18}H_{15}NO_2$. Calculated: C 78.0; H 5.5; N 5.1%.

6,11-Dihydro-5-benzyl-11-oxobenzo[b]carbazole (XII). This compound was obtained in 35.6% yield under the conditions of the synthesis of X and had mp 172-174° (in a sealed capillary, from ethyl acetate) and R_f 0.65. Found: C 85.8; H 5.1; N 4.4%. $C_{23}H_{17}NO$. Calculated: C 85.4; H 5.3; N 4.3%.

6,11-Dioxobenzo[b]carbazoles (XIII-XV). Chromic acid (6 g of chromic anhydride in 6 ml of water) was added to a suspension of 15 mmole of benzo[b]carbazoles X-XII in 120 ml of glacial acetic acid while maintaining the temperature of the reaction mixture at ~15°. The mixture was stirred at 50° for 2 h and cooled. The precipitate was removed by filtration, washed with water, and dried. Dilution of the mother liquor with water gave an additional amount of XIII-XV. Data on the physical constants and yields of XIII-XV are presented in Table 1.

LITERATURE CITED

1. US Patent No. 3,005,827 (1960); Chem. Abstr., 56, 3460 (1962).
2. V. I. Shvedov, G. N. Kurilo, and A. N. Grinev, Khim.-Farmats. Zh., 9, 7 (1970).
3. G. Robinson and R. Robinson, J. Chem. Soc., 827 (1924).
4. N. N. Suvorov, N. P. Sorokina, and Yu. N. Sheinker, Zh. Obshch. Khim., 28, 1090 (1958).
5. F. Millich and E. I. Becker, J. Org. Chem., 23, 1096 (1958).
6. H. Yamamoto, A. Misaki, and M. Imanaka, Chem. Pharm. Bull. (Tokyo), 16, 2313 (1968).
7. N. P. Buu-Hoi, P. Jacquignon, and O. Perin-Roussell, Bull. Soc. Chim. France, 10, 2849 (1965).
8. M. Nakazaki, K. Yamamoto, and K. Yamagami, Bull. Chem. Soc. Japan, 33, 466 (1960).
9. F. Ulig and H. Snyder, in: Advances in Organic Chemistry, R. A. Raphael (editor), Wiley (1960).