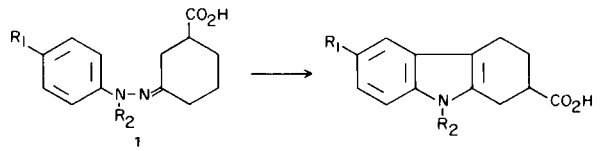
Selectivity in the Fischer Indolization of Phenylhydrazones Derived From 3-Ketocyclohexanecarboxylic Acid

George R. Allen, Jr.

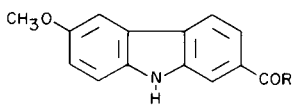
Process and Preparations Research Section
Lederle Laboratories, A Division of American Cyanamid Company

Among the varied procedures for the fabrication of the indole nucleus, the Fischer cyclization of phenylhydrazones assumes premier importance (1). This procedure also has been adapted to the synthesis of 1,2,3,4-tetrahydrocarbazoles and numerous studies have established that *m*-substituted phenylhydrazones of cyclohexanone usually afford mixtures of 5- and 7-substituted-1,2,3,4-tetrahydrocarbazoles (2). Despite the enormity of literature elicited by this synthetic procedure, it is not clear whether phenylhydrazones of 3-substituted cyclohexanones exhibit a similar propensity toward isomer formation. Borsche and his co-workers (4) found that the phenylhydrazone of 3-methylcyclohexanone gave a single product which Barclay and Campbell demonstrated to be 2-methyl-1,2,3,4-tetrahydrocarbazole (5). In an earlier investigation Baeyer and Tutein reported that cyclization of the phenylhydrazone of 3-ketocyclohexanecarboxylic acid, *e.g.*, **1a**, gave a single isomer of undetermined constitution (6). In the present report it is shown that this product is 1,2,3,4-tetrahydrocarbazole-2-carboxylic acid and that Fischer cyclization of phenylhydrazones derived from 3-ketocyclohexanecarboxylic acid proceeds with high selectivity.



Series a: $R_1 = R_2 = H$
Series b: $R_1 = OCH_3$; $R_2 = p\text{-}ClC_6H_4CO$
Series c: $R_1 = OCH_3$; $R_2 = H$

Thus, treatment of hydrazones **1a-c** with hot dilute acetic acid smoothly gave 61-84% of carbazoles **2a-c**, respectively; formation of isomeric products was not detected. The constitution of **2a** was established by dehydrogenation of the derived methyl ester into the known methyl carbazole-2-carboxylate (7). Carbazoles **2b** and **2c** were correlated by base hydrolysis of the former substance to give **2c** and *p*-chlorobenzoic acid. The position of the carboxyl group in **2c** was demonstrated by its conversion into a 6-methoxycarbazolecarboxaldehyde, and comparison of the ultraviolet spectrum of the latter substance with the distinguishing spectra reported for the isomeric 2- and 4-carbazolecarboxaldehydes (8). These comparisons clearly define the aldehyde as the 2-isomer **6** and establish **2c** as the structure of the tetrahydrocarbazolecarboxylic acid.



3: R = OCH_3
4: R = $NHNH_2$
5: R = $NHNHTs$
6: R = H

The conversion of **2c** into **6** was achieved *via* dehydrogenation of the derived methyl ester into **3**. This last substance was converted into the tosylhydrazide **5** *via* hydrazide **4**. Decomposition of **5** by the McFadyen-Stevens technique then gave **6**. The low yield (11%) realized for the conversion of **5** into **6** appears to be characteristic for the preparation of carbazole-2-carboxaldehydes by this procedure (7), and is not considered indicative of the presence of an isomer.

EXPERIMENTAL

General.

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution on a Cary recording spectrophotometer. Infrared spectra were determined in pressed potassium bromide discs on a Perkin-Elmer Model 21 spectrophotometer. All evaporations were carried out under reduced pressure.

1,2,3,4-Tetrahydrocarbazole-2-carboxylic Acid (**2a**).

A mixture of 1.30 g. (10 mmoles) of 3-ketocyclohexanecarboxylic acid (9) and 1.09 g. (10 mmoles, 1 ml.) of phenylhydrazine in 10 ml. of water was heated on the steam bath with agitation for about 10 minutes when the yellow oil crystallized. Acetic acid (16 ml.) was added, and heating was continued for 20 minutes. The resulting mixture was diluted with water, cooled, and filtered to give 1.40 g. (65%) of pale yellow crystals, m.p. 233-235° (lit. (6) m.p. 230°).

Methyl 1,2,3,4-Tetrahydrocarbazole-2-carboxylate.

A solution of 1.40 g. (6.52 mmoles) of 1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (**2a**) and 1 ml. of 98% sulfuric acid in 100 ml. of methanol was heated at reflux temperature for 4 hours. The solution was concentrated under reduced pressure until solid began precipitating and then rendered alkaline with ammonium hydroxide. The mixture was diluted with water, cooled, and filtered to give 1.22 g. (82%) of crystals, m.p. 111-114°. Recrystallization from acetone-hexane gave crystals, m.p. 119°; uv max 227, 282, 290 mμ (ε, 31,400; 6860; 5840); ir 2.97, 5.80, 6.15, 6.26 μ.

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.38; H, 6.66; N, 6.00.

Methyl Carabazole-2-carboxylate.

A stirred mixture of 600 mg. (2.62 mmoles) of methyl 1,2,3,4-tetrahydrocarbazole-2-carboxylate and 350 mg. of 10% palladium-on-carbon in 25 ml. of cumene was heated at reflux temperature for 17 hours. The hot mixture was filtered, and the residue was washed with acetone. The combined filtrate and washings were evaporated, and the residue was recrystallized from methanol to give 463 mg. (78%) of crystals, m.p. 187-188° (lit. (7) m.p. 175-177°); uv max 222, 245, 307, 346, 355 (sh) mμ (ε, 17,100; 45,000; 26,700; 4050; 3600); ir 3.00, 6.12, 6.35 μ.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.45; H, 5.10; N, 6.07.

9-(*p*-Chlorobenzoyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole-2-carboxylic Acid (**2b**).

A mixture of 1.30 g. (10 mmoles) of 3-ketocyclohexanecarboxylic acid and 3.13 mg. (10 mmoles) of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride (10) in 10 ml. of glacial acetic acid was stirred at 75-80° for 2 hours. The cooled mixture was filtered to give 2.97 g. (77%) of white crystals, m.p. 231-234°; uv max 230, 268, 318 mμ (ε, 16,700; 12,900; 5380); ir 2.95, 3.20, 5.88, 5.96, 6.22 μ.

Anal. Calcd. for $C_{21}H_{18}ClNO_4$: C, 65.71; H, 4.73; Cl, 9.24; N, 3.65. Found: C, 65.71; H, 4.84; Cl, 8.99; N, 3.75.

When this experiment was conducted on a 1 mmole-scale, 84% of **2b** was isolated.

6-Methoxy-1,2,3,4-tetrahydrocarbazole-2-carboxylic Acid (**2c**).

A.

A mixture of 383 mg. (1 mmole) of 9-(*p*-chlorobenzoyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (**2b**) and 25 ml. of 0.1*N* sodium hydroxide solution was stirred at ambient temperature for 4 hours. The solution was acidified by addition of hydrochloric acid. The resulting mixture was chilled in an ice-bath and filtered to give 209 mg. of solid which was subjected to partition chromatography on diatomaceous silica using a heptane-ethyl acetate-methanol-water (75:25:17:4) system (11). That fraction eluted at peak hold-back-volume 1.2 (Vm/Vs 2.45) was evaporated, and the residue was recrystallized from acetone-hexane to give 58 mg. (37%) of crystals, m.p. 240.0-241.5°. A mixture of this material with authentic *p*-chlorobenzoic acid melted at 240.0-241.5°. Evaporation of that peak eluted at hold-back-volume 5.8 gave a residue that was recrystallized from acetone-hexane to give 83 mg. (34%) of crystals, m.p. 226-227°; uv max 227, 282, 296 mμ (ε, 25,500; 8200; 6360); ir 2.94, 3.41, 3.75, 5.86, 6.12, 6.25 μ.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.40; H, 5.81; N, 5.37.

B.

A mixture of 1.30 g. (10.0 mmoles) of 3-ketocyclohexanecarboxylic acid and 1.39 g. (10.0 mmoles) of *p*-methoxyphenylhydrazine in 20 ml. of water was heated on the steam-bath for 10 minutes. Acetic acid (20 ml.) was added, and heating was continued for 15 minutes and then diluted with water. Filtration gave 1.48 g. (61%) of solid, m.p. 202-210°. This material was recrystallized from acetone-hexane to give crystals, m.p. 222-224°. Admixture with a sample prepared as described in Method A caused no depression in melting point.

Methyl 1,2,3,4-Tetrahydro-6-methoxycarbazole-2-carboxylate.

Fischer esterification of **2c** (0.53 g.) as described previously gave 0.50 g. (90%) of crystals, m.p. 122-124°. A sample recrystallized from dilute methanol had m.p. 124-125°; uv max 227, 282, 296, 308 (sh) mμ (ε, 27,200; 8950; 8050; 4920); ir 2.95, 5.75, 6.14, 6.25 μ.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.42; H, 6.74; N, 5.25.

Methyl 6-Methoxycarbazole-2-carboxylate (**3**).

Dehydrogenation of 400 mg. (1.6 mmoles) of methyl 1,2,3,4-tetrahydro-6-methoxycarbazole-2-carboxylate with 200 mg. of 10% palladium-on-charcoal as described previously gave a product that was recrystallized from methanol to give 220 mg. (54%) of crystals, m.p. 189-190°, uv max 240, 256, 315, 375 mμ (ε, 30,000; 32,400; 29,600; 4600); ir 3.03, 5.92, 6.20, 6.28, 6.37 μ.

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.24; H, 5.25; N, 5.46.

6-Methoxycarbazole-2-carbohydrazide (**4**).

A mixture of 300 mg. (1.18 mmoles) of **3** and 10 ml. of hydrazine hydrate was heated at reflux temperature for 5 hours. The cooled mixture was diluted with water and filtered to give 200 mg. of solid that was recrystallized from methanol to furnish crystals, m.p. 250-251°.

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.36; H, 4.73; N, 15.99.

p-Toluenesulfonyl-6-methoxycarbazole-2-carbohydrazide (**5**).

A solution of 121 mg. (0.5 mmole) of 6-methoxycarbazole-2-carbohydrazide (4) and 91 mg. (0.5 mmole) of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was allowed to stand at ambient temperature for 6 hours. The solution was poured onto a cracked ice-hydrochloric acid mixture; filtration gave 157 mg. (77%) of solid that was crystallized from methanol to give crystals, m.p. 257-258° dec.; uv max 224, 236, 258, 313, 365 mμ (ε, 29,900; 31,100; 31,100; 26,600; 4910) ir 3.00, 3.12, 6.05, 8.57 μ.

Anal. Calcd. for $C_{21}H_{19}N_3O_4S$: C, 61.60; H, 4.68; N, 10.26; S, 7.81. Found: C, 61.61; H, 4.73; N, 10.57; S, 7.74.

6-Methoxycarbazole-2-carboxaldehyde (**6**).

A stirred mixture of 229 mg. (0.56 mmole) of **5** and 200 mg. of sodium carbonate in 5 ml. of ethylene glycol was heated slowly to 195° over approximately 30 minutes. The cooled mixture was poured into water and extracted with benzene. The combined extracts were dried and evaporated to give a residue that was chromatographed on a synthetic magnesia-silica gel column. The yellow material eluted by benzene was recrystallized from benzene-heptane to give 14 mg. (11%) of bright yellow crystals, m.p. 133-135°; uv max 240 (sh), 253, 280 (sh), 335, 390 mμ (ε, 17,800; 21,000; 11,900; 22,200; 3820); ir 3.01, 5.96; 6.22, 6.30 μ.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.60; H, 4.99; N, 6.29.

Acknowledgment.

The author is indebted to Mr. F. J. McEvoy for a generous sample of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride and to Dr. C. F. Howell for his interest and for helpful discussions. Partition chromatography, spectral data, and microanalyses were performed by Messers. C. Pidacks, W. Fulmor, L. M. Brancone and their associates, respectively.

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Received September 18, 1969 Pearl River, New York 10965