Friedländer Reaction of 3-Acetyltropolone: Synthesis of 3-(2-Quinolyl)tropolones

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3-Acetyltropolone (**1a**) reacted with 2-aminobenzaldehydes in the presence of sodium ethoxide to afford 3-(2-quinolyl)tropolone (**3aa**) in 96% yield. Methyl- and isopropyl-substituted tropolones **1b,c** also gave six 3-(2-quinolyl)tropolones in excellent yields. The compound **3aa** was allowed to stand in 40% aqueous methylamine solution to give 7-methylamino-2-(2-quinolyl)tropone (**4**).

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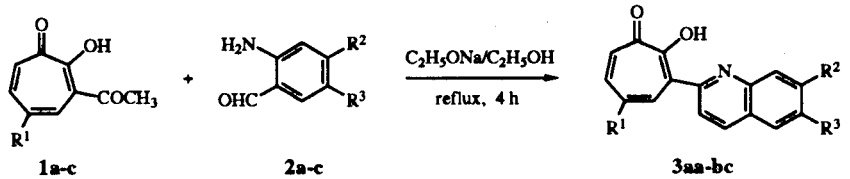
In the field of tropoid chemistry, a number of heterocycle-fused compounds have been reported [1]. However, little is known about tropolone possessing a heterocyclic ring as the side-chain, except for some compounds, such as 4-(3- and 5-pyrazolyl)- [2,3], 4-(5-isoxazolyl)- [3], 3-(4-thiazolyl)- [4,5] and 4-(2-quinolyl)tropolones [6]. Recently, we preliminarily reported that the Friedländer reactions of 3-acetyltropolone (**1a**) and 7-methylamino-2-acetyltropone are useful for the synthesis of 3-(2-quinolyl)tropolone derivatives [7]. Now, our interests on the biological activities of heterocyclic compounds prompted us to synthesis of several 3-(2-quinolyl)tropolones. In order to enhance their lipophilicity, a methyl or isopropyl group was introduced to the tropolone ring. Two methoxy groups or a methylenedioxy group was also introduced to the quinoline ring.

When a solution of 3-acetyltropolones **1a-c** and an equimolecular amount of 2-aminobenzaldehydes **2a-c** in absolute ethanol was refluxed for 4 hours in the presence of sodium ethoxide, the corresponding 3-(2-quinolyl)tropolones **3aa-bc** were obtained in excellent yields (88-96%), except for **3ca** (71%).

The ir spectra of the 3-(2-quinolyl)tropolones **3aa-bc** show typical ν_{OH} and $\nu_{C=O}$ absorption bands for tropolones. Their ^1H and ^{13}C nmr spectra also gave satisfactory results. In the uv spectra of 3-(2-quinolyl)tropolone (**3aa**), four absorption bands were observed at 216, 254, 319, and 374 nm. The last absorption band was deviated to the longer wavelength region than that of tropolone itself. This suggested the contribution of π-π conjugation between two ring systems of the tropolone and the quinoline ring. The introduction of the methoxy group exhibited bathochromic shift.

Scheme 1

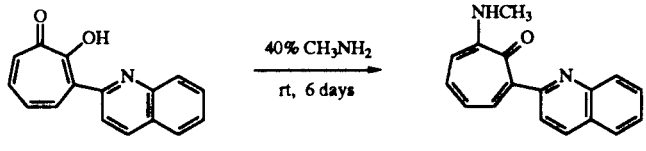


1a-c **2a-c** **3aa-bc**

a	$R^1 = H$	**a**	$R^2 = R^3 = H$	**aa**	$R^1 = R^2 = R^3 = H$
b	$R^1 = CH_3$	**b**	$R^2 = R^3 = OCH_3$	**ba**	$R^1 = CH_3$, $R^2 = R^3 = H$
c	$R^1 = CH(CH_3)_2$	**c**	$R^2, R^3 = OCH_2O$	**ca**	$R^1 = CH(CH_3)_2$, $R^2 = R^3 = H$
				ab	$R^1 = H$, $R^2 = R^3 = OCH_3$
				bb	$R^1 = CH_3$, $R^2 = R^3 = OCH_3$
				ac	$R^1 = H$, $R^2, R^3 = OCH_2O$
				bc	$R^1 = CH_3$, $R^2, R^3 = OCH_2O$

Generally, tropolones do not react with nucleophiles. 3-(2-Quinolyl)tropolone (**3aa**) was allowed to stand for 6 days in 40% aqueous methylamine solution to afford 7-

Scheme 2



3aa **4**

methylamino-2-(2-quinolyl)tropone (**4**) [7] (87%) as a sole product. This means that the tropolone nucleus of the compound **3aa** is unusually activated by the electron-defficient quinoline ring for the nucleophilic attack of methylamine.

EXPERIMENTAL

Measurements.

All melting points were determined with a Yanagimoto MP-S2 micro-melting point apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer, and the uv spectra on a Hitachi U-3210 spectrophotometer. The ^1H and ^{13}C nmr spectra were measured with a JEOL JMN-EX90 spectrometer (90 MHz for ^1H and 22.5 MHz for ^{13}C nmr) using tetramethylsilane as internal standard.

Materials.

3-Acetyltropolones **1a** [8], **b** [9], and **c** [9] were obtained in the literature methods. 2-Aminobenzaldehydes **2a** [10], **b** [11], and **c** [12] were synthesized by the reduction of the corresponding 2-nitrobenzaldehyde, 4,5-dimethoxy-2-nitrobenzaldehyde and 4,5-methylenedioxy-2-nitrobenzaldehyde with iron powder in hydrochloric acid. The first and the last nirobenzaldehydes are commercially available and the middle one was prepared according to the literature [13].

Reactions of 3-Acetyltropolones **1a-c** with 2-Aminobenzaldehydes **2a-c**.

To a solution of 3-acetyltropolones **1a-c** (1.0 mmole) and 2-aminobenzaldehydes **2a-c** (1.0 mmole) in absolute ethanol (6 ml) was added a solution of sodium ethoxide, prepared from sodium (46 mg, 2.0 mmoles) and absolute ethanol (2 ml). The mixture was refluxed for 4 hours, cooled to room temperature, quenched with water, acidified with 2*M* hydrochloric acid, extracted thrice with chloroform (3 x 30 ml). The combined extract was dried over sodium sulfate and evaporated to dryness. The resulting solid was chromatographed on a Wakogel C-200 column (10 g) with chloroform/methanol (100:2 v/v) to afford 3-(2-quinolyl)tropolones **3aa-bc** as follows.

3-(2-Quinolyl)tropolone (**3aa**).

This compound was obtained in a yield of 239 mg (96%) as yellow needles (from methanol), mp 172-173° (lit [7], 169-170°); ir (potassium bromide): ν max 3550 (OH), 1601 cm^{-1} (C=O); uv (methanol); λ max 216 (log ε 4.37), 254 (4.36), 319 (3.93), 374 nm (3.88); ^1H nmr (deuteriochloroform): δ 7.10-8.25 (10H, m); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 120.8 (=CH-), 123.0 (=CH-), 126.7 (=CH-), 126.9 (4'-C), 127.1 (=CH-), 127.7 (=CH-), 128.8 (=CH-), 129.5 (=CH-), 135.1 (=CH-), 137.6 (=CH-), 137.8 (=C<), 140.2 (=CH-), 147.4 (8' a-C), 158.2 (=C<), 170.3 (1-C or 2-C), 172.5 (1-C or 2-C).

5-Methyl-3-(2-quinolyl)tropolone (**3ba**).

This compound was obtained in a yield of 239 mg (91%) as yellow needles (from methanol), mp 153-154°; ir (potassium bromide): ν max 3220 (OH), 1616 cm^{-1} (C=O); uv (methanol): λ max 214 (log ε 4.42), 256 (4.39), 318 (3.93), 379 nm (3.91); ^1H nmr (deuteriodimethyl sulfoxide): δ 2.46 (3H, s, CH_3), 7.29 (2H, s, 6,7-H), 7.43-7.96 (4H, m, 5',6', 7',8'-H), 7.87 (1H, d, J = 8.6 Hz, 4'-H), 8.11 (1H, s, 4-H), 8.16 (1H, d, J = 8.6 Hz, 3'-H), 8.91 (1H, br, OH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 25.4 (CH_3), 120.9 (=CH-), 123.1 (=CH-), 126.7 (=CH-), 126.9 (4'-C), 127.7 (=CH-), 128.9 (=CH-), 129.5 (=CH-), 135.0 (=CH-), 137.1 (=C<), 137.4 (=CH-), 137.6 (=C<), 141.4 (=CH-), 147.4 (8' a-C), 158.5 (2'-C), 168.9 (1-C or 2-C), 171.4 (1-C or 2-C).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.33; H, 4.98; N, 5.51.

5-Isopropyl-3-(2-quinolyl)tropolone (**3ca**).

This compound was obtained in a yield of 207 mg (71%) as yellow prisms (from methanol), mp 139-140°; ir (potassium bromide): ν max 3550 (OH), 1600 cm^{-1} (C=O); uv (methanol): λ max 212 (log ε 4.46), 232 (4.44), 251 (4.41), 309 (3.95), 319 (3.98), 376 nm (3.90); ^1H nmr (deuteriodimethyl sulfoxide): δ 1.33 (6H, d, J = 6.9 Hz, 2 x CH_3), 3.05 (1H, sept, J = 6.9 Hz, -CH<), 7.50 (2H, s, 6,7-H), 7.96 (1H, d, J = 8.5 Hz, 4'-H), 8.06 (1H, s, 4-H), 7.54-8.14 (4H, m, 5',6',7',8'-H), 8.49 (1H, d, J = 8.5 Hz, 3'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 23.4 (2 x CH_3), 37.1 (-CH<), 121.5 (=CH-), 123.2 (=CH-), 126.7 (=CH-), 127.0 (4' a-C), 127.6 (=CH-), 128.9 (=CH-), 129.5 (=CH-), 135.0 (2 x =CH-), 137.8 (3-C), 139.4 (=CH-), 147.2 (=C<), 147.4 (8' a-C), 158.7 (2'-C), 169.1 (1-C or 2-C), 171.2 (1-C or 2-C).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.81. Found: C, 78.15; H, 5.86; N, 4.96.

3-(6,7-Dimethoxyquinol-2-yl)tropolone (**3ab**).

This compound was obtained in a yield of 297 mg (96%) as orange-yellow needles (from methanol), mp 220-221°; ir (potassium bromide): ν max 3430 (OH), 1620 cm^{-1} (C=O); uv (methanol): λ max 230 (log ε 4.52), 248 (4.44), 340 (4.14), 360 (4.09), 375 (4.05), 452 (3.48), 480 nm (3.41); ^1H nmr (deuteriochloroform): δ 4.04 (6H, s, 2 x OCH_3), 7.09 (1H, s, 5'-H), 7.16-7.40 (3H, m, 5,6,7-H), 7.46 (1H, s, 8'-H), 7.83 (1H, d, J = 8.5 Hz, 4'-H), 8.07 (1H, d, J = 8.5 Hz, 3'-H), 8.18 (1H, m, 4-H); ^{13}C nmr (deuteriochloroform): δ 56.1 (OCH_3), 56.2 (OCH_3), 104.9 (5'-C), 108.0 (8'-C), 121.1 (=CH-), 122.1 (=CH-), 123.2 (=C<), 127.4 (=CH-), 133.9 (=CH-), 136.3 (=C<), 137.7 (=CH-), 140.9 (=CH-), 144.9 (=C<), 150.3 (=C<), 152.7 (=C<), 155.0 (2'-C), 171.6 (1-C or 2-C), 171.8 (1-C or 2-C).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.05; H, 4.86; N, 4.68.

5-Methyl-3-(6,7-dimethoxyquinol-2-yl)tropolone (**3bb**).

This compound was obtained in a yield of 304 mg (94%) as yellow needles (from methanol), mp 213-214°; ir (potassium bromide): ν max 3440 (OH), 1621 cm^{-1} (C=O); uv (methanol): λ max 234 (log ε 4.54), 326 (4.14), 335 (4.17), 380 nm (4.06); ^1H nmr deuteriochloroform): δ 2.50 (3H, s, CH_3), 4.04 (6H, s, 2 x OCH_3), 7.08 (1H, s, 5'-H), 7.32 (2H, s, 6,7-H), 7.48 (1H, s, 8'-H), 7.77 (1H, d, J = 8.5 Hz, 4'-H), 7.97 (1H, s, 4-H), 8.05 (1H, d, J = 8.5 Hz, 3'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 56.0 (OCH_3), 56.1 (OCH_3), 104.9 (5'-C), 108.1 (8'-C), 121.3 (=CH-), 122.0 (=CH-), 123.1 (=C<), 133.7 (=CH-), 136.6 (=C<), 138.0 (=C<), 138.2 (=CH-), 142.2 (=CH-), 145.1 (=C<), 150.2 (=C<), 152.6 (=C<), 155.5 (2'-C), 170.2 (1-C or 2-C), 170.4 (1-C or 2-C).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.78; H, 5.22; N, 4.40.

3-(6,7-Methylenedioxyquinol-2-yl)tropolone (**3ac**).

This compound was obtained in a yield of 270 mg (92%) as yellow needles (from methanol-chloroform), mp 230-231° (lit

[7] 211-212°); ir (potassium bromide): ν max 3500 (OH), 1619 cm^{-1} (C=O); uv (methanol): λ max: 231 (log ε 4.49), 324 (4.00), 340 (4.07), 357 (4.04), 375 (3.93), 450 nm (3.41); ^1H nmr (deuteriochloroform): δ 6.13 (2H, s, CH_2), 7.11 (1H, s, 5'-H), 7.18-7.49 (3H, m, 5,6,7-H), 7.42 (1H, s, 8'-H), 7.83 (1H, d, J = 8.5 Hz, 4'-H), 8.04 (1H, d, J = 8.5 Hz, 3'-H), 8.15 (1H, d, J = 9.5 Hz, 4-H); ^{13}C nmr (deuteriochloroform): δ 101.8 (OCH_2O), 102.6 (5'-C), 105.9 (8'-C), 121.3 (=CH-), 122.0 (=CH-), 124.7 (=C<), 127.5 (=CH-), 134.5 (=CH-), 136.2 (=C<), 137.8 (=CH-), 141.1 (=CH-), 146.3 (=C<), 148.3 (=C<), 150.9 (=C<), 155.0 (2'-C), 171.6 (1-C + 2-C).

5-Methyl-3-(6,7-methylenedioxyquinol-2-yl)tropolone (**3bc**).

This compound was obtained in a yield of 270 mg (88%) as greenish yellow needles (from methanol), mp 213-214°; ir (potassium bromide): ν max 3420 (OH), 1620 cm^{-1} (C=O); uv (methanol): λ max 223 (log ε 4.56), 337 (4.17), 381 nm (4.05); ^1H nmr (deuteriochloroform): δ 2.50 (3H, s, CH_3), 6.11 (2H, s, OCH_2O), 7.09 (1H, s, 5'-H), 7.31 (2H, s, 6,7-H), 7.43 (1H, s, 8-H), 7.77 (1H, d, J = 8.5 Hz, 4'-H), 7.96 (1H, s, 4-H), 8.01 (1H, d, J = 8.5 Hz, 3'-H); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 101.8 (OCH_2O), 102.6 (5'-C), 105.9 (8'-C), 121.4 (=CH-), 121.9 (=CH-), 124.6 (=C<), 134.4 (=CH-), 136.6 (=C<), 138.1 (=C<), 138.3 (=CH-), 142.4 (=CH-), 146.4 (=C<), 148.3 (=C<), 150.8 (=C<), 155.5 (2'-C), 170.1 (1-C or 2-C), 170.4 (1-C or 2-C).

Anal. Calcd. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.37; H, 4.29; N, 4.70.

Reaction of 3-(2-Quinolyl)tropolone (**3aa**) with Methylamine.

A suspended solution of 3-(2-quinolyl)tropolone (**3aa**) (59 mg, 0.24 mmole) in 40% aqueous methylamine (3 ml) was stirred for 6 days at room temperature. The mixture was quenched with water (5 ml) and extracted thrice with chloroform (3 x 15 ml). The combined extract was concentrated and chromatographed on a Wakogel B-10 plate (20 x 20 cm) with ethyl acetate to give 7-methylamino-2-(2-quinolyl)tropone (**4**) (55 mg, 87%) as orange crystals (from ethanol), mp 193-194° (lit [7] 191-192°); ir (potassium bromide): ν max: 3280 (NH), 1595 cm^{-1} (C=O); uv (methanol): λ max: 213 (log ε 4.53), 233 (4.50), 247 (4.46), 318 (3.85), 350 (3.98), 420 nm (4.30); ^1H nmr (deuteriodimethyl sulfoxide): δ 3.15 (3H, d, J = 5.1 Hz, CH_3), 6.83 (1H, d, J = 10.4 Hz, 6-H), 7.55 (1H, d, J = 10.1 Hz, 3-H), 7.70-8.19 (7H, m, 4,5,4',5',6',7',8'-H), 8.38 (1H, d, J = 8.5 Hz, 3'-H); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 29.6 (CH_3), 108.5 (=CH-), 120.1 (=CH-), 123.9 (=CH-), 126.2 (=CH-), 126.8 (=C<), 127.6 (=CH-), 128.8 (=CH-), 129.1 (=CH-), 134.1 (=CH-), 136.3 (=C<), 137.4 (=CH-), 139.2 (=CH-), 147.6 (=C<), 158.4 (2'-C), 160.6 (7-C), 173.7 (1-C).

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