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Synthesis of Some 3-Cyano-2-methylquinolin-4-ones

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The condensation of ethyl 2-cyano-3-ethoxycrotonate with various anilines gave the corresponding anilinocrotonates which were cyclized in refluxing Dowtherm "A" to give the title quinolones.

[Keywords: Ethyl 3-anilino-2-cyanocrotonates; Ethyl 2-cyano-3-ethoxycrotonate; Gould-Jacobs reaction; Quinolines]

Synthese einiger 3-Cyano-2-methylchinolin-4-one

Die Titelverbindungen wurden mittels Kondensation von Ethyl-2-cyano-3-ethoxycrotonat mit verschiedenen Anilinen zu den entsprechenden Anilincrotonaten und deren Cyclisierung mit Duratherm „A" am Rückfluß hergestellt.

Introduction

Various quinolin-4-ones which bear a carboxyl group in the 3 position have been shown to be good antibacterial agents and some of these such as nalidixic acid[2] and oxolinic acid[3] are in clinical use. The synthesis of these quinolones use 3-ethoxyacrylates derived from malonic ester or other active methylene compounds in a *Gould-Jacobs* reaction[4]. The use of the corresponding crotonates in this reaction could lead to 2-methyl derivatives of quinolin-4-one which could also be of interest. Literature search revealed that ethyl 2-cyano-3-ethoxycrotonate (**1**) although reported some years ago[5] has not been employed for such synthesis. In continuing our work on the use of *Gould-Jacobs* reaction[6], we are extending the synthesis of quinolines using this crotonate as outlined in the scheme 1.

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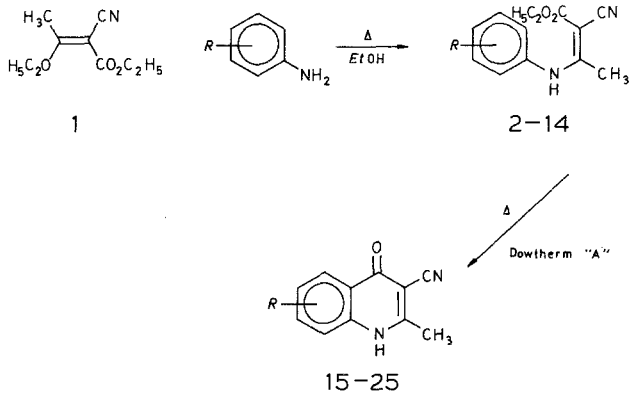
Scheme 1



Results and Discussion

1 was prepared from the reaction of triethyl orthoacetate and ethyl cyanoacetate in the presence of acetic anhydride[5]. The condensation of **1** with various anilines in refluxing ethanol gave the corresponding anilinocrotonates (**2**—**11**, **13**, and **14**). The anilinocrotonate (**12**) could only be obtained by condensation of *o*-nitroaniline and **1** at 180°. Some of these anilinocrotonates (**2**, **5**, **8**, **11**, and **14**) are reported in the literature as by-products in the synthesis of cyclic amidines from ethyl 2-cyano-3-oxobutyrate[7].

The anilinocrotonates (**2**—**14**) on heating in Dowtherm "A" under reflux, in majority of the cases, cyclized to give the corresponding quinolin-4-ones (**15**—**25**) in good yields. The anilinocrotonates (**12** and **13**), however, did not cyclize under these conditions.

Acknowledgements

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Experimental

The proton magnetic resonance spectra (PMR) were obtained on a Hitachi Perkin-Elmer model R-20 B spectrometer operating at 60 MHz (*TMS* as internal standard). The infrared (IR) absorption spectra were taken by the Perkin-Elmer model 727 spectrophotometer. The samples were measured in potassium bromide disks. Melting points (m.p.) were determined with a Fisher-Johns apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer model 240 and are in full agreement with the calculated values.

Ethyl 3-N-anilino-2-cyanocrotonates (**2**—**14**)

General Method. Equimolar quantities of an aniline and ethyl 2-cyano-3-ethoxycrotonate (**1**) were heated under reflux in ethanol for a period of 3 to 4 h. On cooling the desired anilinocrotonate was filtered and purified by crystallization from aqueous ethanol.

Ethyl 3-N-anilino-2-cyanocrotonate (**2**): m.p. 113–115° (lit.[7] m.p. 83–84°); yield 48%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1660 (C=O); PMR δ (CCl_4): 1.35 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.25 (3H, s, CH_3), 4.22 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 7.00–7.30 (5H, m, H-2–H-6), 11.54 (1H, br., NH).

Ethyl 2-cyano-3-N-o-toluidinocrotonate (**3**): $C_{14}H_{16}N_2O_2$; m.p. 109–112°; yield 57%; IR (cm^{-1}): 3180 (NH), 2200 (C≡N), 1660 (C=O); PMR δ ($CDCl_3$): 1.31 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.15 (3H, s, CH_3), 2.27 (3H, s, CH_3), 4.23 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 7.00–7.35 (4H, m, H-3 and H-5), 11.34 (1H, br., NH).

Ethyl 2-cyano-3-N-m-toluidinocrotonate (**4**); $C_{14}H_{16}N_2O_2$; m.p. 72–73°; yield 50%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1650 (C=O); PMR δ (CCl_4): 1.32 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.23 (3H, s, CH_3), 2.37 (3H, s, CH_3), 4.19 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 6.90–7.30 (4H, m, H-2, H-4, H-5, and H-6), 11.48 (1H, br., NH).

Ethyl 2-cyano-3-N-p-toluidinocrotonate (**5**): m.p. 104–106° (lit.[7] m.p. 109–110°); yield 45%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1670 (C=O); PMR δ ($CDCl_3$): 1.34 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.25 (3H, s, CH_3), 2.40 (3H, s, CH_3), 4.27 (2H, q, $J = 7.5$ Hz, O—CH_2—CH_3), 7.00 (2H, d, $J = 9.0$ Hz, H-2 and H-6), 7.26 (2H, d, $J = 9.0$ Hz, H-3 and H-5), 11.45 (1H, br., NH).

Ethyl 3-N-o-chloroanilino-2-cyanocrotonate (**6**): $C_{13}H_{13}ClN_2O_2$; m.p. 135–137°; yield 29%; IR (cm^{-1}): 3200 (NH), 2210 (C≡N), 1660 (C=O); PMR δ ($CDCl_3$): 1.35 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.23 (3H, s, CH_3), 4.26 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 7.10–7.60 (5H, m, H-2–H-6), 11.44 (1H, br., NH).

Ethyl 3-N-m-chloroanilino-2-cyanocrotonate (**7**): $C_{13}H_{13}ClN_2O_2$; m.p. 140–143°; yield 53%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1670 (C=O); PMR δ ($CDCl_3$): 1.41 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.28 (3H, s, CH_3), 4.32 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 7.00–7.50 (4H, m, H-2, H-4, H-5, and H-6), 11.63 (1H, br., NH).

Ethyl 3-N-p-chloroanilino-2-cyanocrotonate (**8**): m.p. 142–144° (lit.[7] m.p. 147–148°); yield 53%; IR (cm^{-1}): 3220 (NH), 2200 (C≡), 1670 (C=O); PMR δ ($CDCl_3$): 1.36 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.28 (3H, s, CH_3), 4.28 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 7.09 (2H, d, $J = 9.0$ Hz, H-2 and H-6), 7.41 (2H, d, $J = 9.0$ Hz, H-3 and H-5), 11.52 (1H, br., NH).

Ethyl 3-N-o-anisidino-2-cyanocrotonate (**9**): $C_{14}H_{16}N_2O_3$; m.p. 61–63°; yield 28%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1665 (C=O); PMR δ ($CDCl_3$): 1.28 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.17 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.20 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 6.80–7.30 (4H, m, H-3, H-4, H-5, and H-6), 11.25 (1H, br., NH).

Ethyl 3-N-m-anisidino-2-cyanocrotonate (**10**): $C_{14}H_{16}N_2O_3$; m.p. 96–97°; yield 51%; IR (cm^{-1}): 3200 (NH), 2200 (C≡N), 1665 (C=O); PMR δ ($CDCl_3$): 1.34 (3H, t, $J = 7.5$ Hz, —O—CH_2—CH_3), 2.29 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.25 (2H, q, $J = 7.5$ Hz, —O—CH_2—CH_3), 6.66–7.50 (4H, m, H-2, H-4, H-5, and H-6), 11.50 (1H, br., NH).

Ethyl 3-N-p-anisidino-2-cyanocrotonate (**11**): m.p. 118-119° (lit.[7] m.p. 115-117°); yield 51%; IR (cm^{-1}): 3210 (NH), 2200 (C≡N), 1655 (C=O); PMR δ ($CDCl_3$): 1.24 (3H, t, J = 7.5 Hz, —O—CH_2—C**H**$_3$), 2.10 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.12 (2H, q, J = 7.5 Hz, —O—C**H**$_2$—CH_3), 6.73 (2H, d, J = 9.0 Hz, H-3 and H-5), 6.96 (2H, d, J = 9.0 Hz, H-2 and H-6), 11.37 (1H, br., NH).

Ethyl 2-cyano-3-N-o-nitroanilinocrotonate (**12**): This was obtained by the condensation of *o*-nitroaniline with **1** under reduced pressure (10 mm) in the absence of ethanol and at a temperature of 180° (silicone bath). $C_{13}H_{13}N_3O_4$; m.p. 112-114°; yield 34%; IR (cm^{-1}): 3100 (NH), 2210 (C≡N), 1660 (C=O), 1520 and 1330 (NO_2); PMR δ ($CDCl_3$): 1.35 (3H, t, J = 7.5 Hz, —O—CH_2—C**H**$_3$), 2.34 (3H, s, CH_3), 4.32 (2H, q, J = 7.5 Hz, —O—C**H**$_2$—CH_3), 7.20-7.90 (3H, m, H-4, H-5, and H-6), 8.12 (1H, dd, J = 1.0 Hz and 9.0 Hz, H-3), 12.24 (1H, br., NH).

Ethyl 2-cyano-3-N-m-nitroanilinocrotonate (**13**): $C_{13}H_{13}N_3O_4$; m.p. 138-140°; yield 27%; IR (cm^{-1}): 3190 (NH), 2210 (C≡N), 1680 (C=O), 1525 and 1340 (NO_2); PMR δ ($CDCl_3$): 1.35 (3H, t, J = 7.5 Hz, —O—CH_2—C**H**$_3$), 2.36 (3H, s, CH_3), 4.28 (2H, q, J = 7.5 Hz, —O—C**H**$_2$—CH_3), 7.50-8.30 (4H, m, H-2, H-4, H-5, and H-6), 11.72 (1H, br., NH).

Ethyl 2-cyano-3-N-p-nitroanilinocrotonate (**14**): m.p. 167-168° (lit.[7] m.p. 170-175°); yield 25%; IR (cm^{-1}): 3100 (NH), 2215 (C≡N), 1660 (C=O), 1585 and 1345 (NO_2); PMR δ ($CDCl_3$): 1.38 (3H, t, J = 7.5 Hz, —O—CH_2—C**H**$_3$), 2.42 (3H, s, CH_3), 4.27 (2H, q, J = 7.5 Hz, —O—C**H**$_2$—CH_3), 7.28 (2H, d, J = 9.0 Hz, H-2 and H-6), 8.28 (2H, d, J = 9.0 Hz, H-3 and H-5), 11.88 (1H, br., NH).

Quinolin-4-ones (**15-25**)

General method. To 5 ml of refluxing Dowtherm "A", 1 g of the anilinocrotonate (**2-14**) was added in small portions and let heat under reflux for a period of 2 to 3 h. On cooling, the reaction mixture was precipitated with petroleum ether (b.p. 40-60°), filtered, washed with petroleum ether and crystallized from an appropriate solvent.

3-Cyano-2-methyl-1H-quinolin-4-one (**15**): m.p. > 300° (*Ac*OH) (lit.[7] m.p. 360-365° dec.); yield 87%; IR (cm^{-1}): 3260, 3220 (NH), 2220 (C≡N), 1628 (C=O); PMR δ (CF_3CO_2H): 3.12 (3H, s, CH_3), 7.80-8.30 (3H, m, H-6-H-8), 8.61 (1H, dd, J = 1.5 and 8.0 Hz, H-5).

3-Cyano-2,8-dimethyl-1H-quinolin-4-one (**16**): $C_{12}H_{10}N_2O$; m.p. > 300° (*DMSO*-H_2O); yield 75%; IR (cm^{-1}): 3260 (NH), 2220 (C≡N), 1610 (C=O); PMR δ (CF_3CO_2H): 2.88 (3H, s, CH_3), 3.22 (3H, s, CH_3), 7.95 (2H, m, H-6 and H-7), 8.58 (1H, dd, J = 1.5 and 9.0 Hz, H-5).

3-Cyano-2,7-dimethyl-1H-quinolin-4-one (**17**): $C_{12}H_{10}N_2O$; m.p. 260 (dec.) (*DMSO*-H_2O); yield 72%; IR (cm^{-1}): 3270 (NH), 2220 (C≡N), 1640 (C=O).

3-Cyano-2,6-dimethyl-1H-quinolin-4-one (**18**): m.p. > 300° (*DMSO*-H_2O) (lit.[7] m.p. 345-360° (dec.); yield 38%; IR (cm^{-1}): 3260 and 3220 (NH), 2220 (C≡N), 1620 (C=O); PMR δ (CF_3CO_2H): 2.71 (3H, s, CH_3), 3.12 (3H, s, CH_3), 8.01 (2H, s, H-7 and H-8), 8.39 (1H, s, H-5).

8-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (**19**): $C_{11}H_7ClN_2O$; m.p. 297° (dec.) (*Ac*OH); yield 22%; IR (cm^{-1}): 3230 (NH), 2220 (C≡N), 1610 (C=O); PMR δ (CF_3CO_2H): 3.10 (3H, s, CH_3), 7.80 (1H, d, J = 8.0 Hz, H-6), 8.15 (1H, dd, J = 1.5 and 8.0 Hz, H-7), 8.48 (1H, dd, J = 1.5 and 8.0 Hz, H-5).

7-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (**20**): $C_{11}H_7ClN_2O$; m.p. > 300° (*DMSO*-H_2O); yield 56%; IR (cm^{-1}): 3250, 3200 (NH), 2224 (C≡N), 1630 (C=O); PMR δ (CF_3CO_2H): 3.09 (3H, s, CH_3), 7.86 (1H, dd, J = 1.5 and 9.0 Hz, H-6), 8.03 (1H, d, J = 1.5 Hz, H-8), 8.56 (1H, d, J = 9.0 Hz, H-5).

6-Chloro-3-cyano-2-methyl-1H-quinolin-4-one (**21**): m.p. > 300° (*DMSO*) (lit.[7] m.p. 350–360° dec.); yield 71%; IR (cm^{-1}): 3250 and 3200 (NH), 2225 (C≡N), 1630 (C=O); PMR δ (CF_3CO_2H): 3.08 (3H, s, CH_3), 7.90–8.10 (2H, m, H-7 and H-8), 8.51 (1H, d, J = 1.5 Hz, H-5).

3-Cyano-8-methoxy-2-methyl-1H-quinolin-4-one (**22**): $C_{12}H_{10}N_2O_2$; m.p. > 300° (*Ac*OH); yield 62%; IR (cm^{-1}): 3200 (NH), 2218 (C≡N), 1620 (C=O); PMR δ (CF_3CO_2H): 3.19 (3H, s, CH_3), 4.24 (3H, s, OCH_3), 7.50–8.05 (2H, m, H-6 and H-7), 8.17 (1H, d, J = 9.0 Hz, H-5).

3-Cyano-7-methoxy-2-methyl-1H-quinolin-4-one (**23**): $C_{12}H_{10}N_2O_2$; m.p. > 300° (*DMSO*); yield 73%; IR (cm^{-1}): 3230 (NH), 2220 (C≡N), 1630 (C=O); PMR δ (CF_3CO_2H): 3.10 (3H, s, CH_3), 4.12 (3H, s, OCH_3), 7.35 (1H, d, J = 1.5 Hz, H-8), 7.50 (1H, dd, J = 1.5 and 9.0 Hz, H-6), 8.48 (1H, d, J = 9.0 Hz, H-5).

3-Cyano-6-methoxy-2-methyl-1H-quinolin-4-one (**24**): m.p. > 300° (*DMSO*-H_2O) (lit.[7] m.p. 350–360° dec.); yield 44%; IR (cm^{-1}): 3250 and 3210 (NH), 2220 (C≡N), 1615 (C=O); PMR δ (CF_3CO_2H): 3.08 (1H, s, CH_3), 4.08 (3H, s, OCH_3), 7.89 (3H, m, H-5, H-7, and H-8).

3-Cyano-2-methyl-7-nitro-1H-quinolin-4-one (**25**): $C_{11}H_7N_3O_3$; m.p. > 300° (*DMSO*-H_2O); yield 32%; IR (cm^{-1}): 3250 and 3200 (NH), 2224 (C≡N), 1635 (C=O), 1550 and 1350 (NO_2); PMR δ (*DMSO*-d_6): 2.60 (3H, s, CH_3), 7.90–8.25 (2H, m, H-5 and H-6), 8.35 (1H, d, J = 1.5 Hz, H-8).

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[1] Taken in part from the Masters Thesis of *T. C. M. Jorge*, Instituto Militar de Engenharia, Rio de Janeiro, March 1981.

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