Reactions of Nitriles. Part VIII.[1] Synthesis of 2,3-Dihydroquinolin-4(1*H*)-ones

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Cyanoethylation of several substituted anilines has been investigated. The resulting nitriles were hydrolysed to the corresponding acids, which on cyclisation afforded 2,3-dihydroquinolin-4(1*H*)-ones, whose structures were established on the basis of their spectra.

In connection with a project involving the use of cyanoethylation in the synthesis of polynuclear heterocyclic compounds, we studied the cyanoethylation of some substituted anilines; this led us to the synthesis of new quinolones. Some quinolones are reported to possess a powerful analgesic activity.[1]

The cyanoethylation of various alkyl- and alkoxy-anilines was carried out with acrylonitrile (1 mol. equiv.) in acetic acid. The reaction, which presumably takes place *via* a Michael type of addition, yielded the corresponding β-anilinopropiononitriles in good yields. Dichloroanilines, however, were cyanoethylated only in the presence of glacial acetic acid and copper(I) chloride as catalyst; no reaction occurred with acetic acid alone.

Hydrolysis of the nitriles produced with aqueous alkali or dilute hydrochloric acid yielded the corresponding β-anilinopropionic acids. Cyclisation of the latter with polyphosphoric acid afforded 2,3-dihydroquinolin-4(1*H*)-ones, which were characterised by the preparation of their 2,4-dinitrophenylhydrazones and identified on the basis of their n.m.r. spectra.

The 3-substituted and 3,4-disubstituted β-anilinopropionic acids yield two isomers, by cyclisation in the two possible directions. These isomers could be easily distinguished on the basis of the aromatic signals in their n.m.r. spectra. The 5-substituted quinolones all show two doublets (each split again into a doublet), due to the C-6 and C-8 protons, coupled with the C-7 proton and with one another. The spectra also show a triplet assigned to the C-7 proton, coupled with the C-6 and C-8 protons. In the case of 5-methylquinolone, the methyl signal appears downfield owing to deshielding by the carbonyl group. The 7-substituted quinolones show two doublets due to the C-5 and C-8 protons, both coupled to the C-6 proton, which gives rise to a doublet of doublets.

The 5,6-disubstituted quinolones give rise to a pair of doublets assigned to the C-7 and C-8 protons, coupled to one another. In 6,7-disubstituted quinolones two singlets are obtained for the C-5 and C-8 protons.

The C-2 and C-3 methylene protons in all the foregoing quinolones resonate as triplets (δ *ca.* 3·2—3·5 and *ca.* 2·4—2·6 p.p.m., respectively). These values agree with those reported [2] for 7-methoxyquinolone. In the case of the alkyl quinolones the NH signal is generally near δ 4·5, whereas in the dichloroquinolones the signal appears near δ 6·7 p.p.m.

The acids (5), (13), and (18) (Table 2) on cyclisation yielded a mixture of quinolones (Table 3) which were separated by chromatography over alumina. However, from the acids (2) and (8) only one isomer could be isolated in each case. A structure was assigned to each quinolone on the basis of its n.m.r. spectrum.

The i.r. spectra (Nujol) of all the quinolones showed bands at *ca.* 1640—1650 (C=O) and 3350—3500 cm^{-1} (NH).

EXPERIMENTAL

Cyanoethylation of Alkyl- and Alkoxy-anilines.—A mixture of the alkyl- or alkoxy-aniline (0·1 mol), glacial acetic acid (2·5 ml), and acrylonitrile (0·1 mol) was heated on a water-bath for 20—24 h. A solution of the product in chloroform was washed with water, saturated aqueous sodium hydrogen carbonate, and then water again, dried (Na_2SO_4), and evaporated to leave the cyanoethyl derivative (Table 1).

Cyanoethylation of Dichloroanilines.—A mixture of the dichloroaniline (0·1 mol), acrylonitrile (0·1 mol), glacial acetic acid (50 ml), and copper(I) chloride (500 mg) was heated on a water-bath for 12 h, cooled, and decomposed with liquid ammonia. A pasty solid separated which was filtered off and washed with water. The solid was dissolved in excess of ether and charcoal was added; the solution was left overnight and filtered. Removal of the solvent yielded the cyanoethyl derivative (Table 1).

Hydrolysis of β-Anilinopropiononitriles.—The cyanoethyl derivative (1 g) was heated under reflux with aqueous 10% potassium hydroxide (50 ml) until there was no further

[1] M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearien, and R. W. Morris, *J. Medicin. Chem.*, 1965, **8**, 566.

[2] W. N. Speckamp, U. K. Pandit, and H. O. Huisman, *Tetrahedron Letters*, 1964, 3279.

evolution of ammonia. The mixture was cooled, acidified initially with conc. hydrochloric acid and then with acetic acid to pH 5·8, and extracted with chloroform. The extract was washed with water, dried, and evaporated to leave the required acid.

When no product was obtained on extraction, the solution was evaporated to dryness (no. 8) and the residue extracted with boiling chloroform; the solution was filtered, dried, and evaporated to yield the acid.

Some of the acids were also obtained by acidic hydrolysis. The cyanoethyl derivative (1 g) was refluxed with conc. hydrochloric acid (30 ml) and water (5 ml) for 3 h. The mixture was cooled, neutralised with liquid ammonia to pH 5·8, and worked up as before (Table 2).

Cyclisation of β-Anilinopropionic Acids.—The acid was added to a mixture of phosphoric oxide (10·0 g for 300 mg of acid) and phosphoric acid (4·0 ml) preheated to 100° (30 min). The mixture was kept at 100° for 2 h with occasional shaking. Water was added and the solid which separated was filtered off, washed with water, saturated aqueous sodium hydrogen carbonate, and then water again, to give the 2,3-dihydroquinolin-4(1*H*)-one (Table 3).

The acid (5) (Table 2) yielded a mixture which was separated by chromatography on alumina. Elution with 3 : 2 light petroleum (b.p. 40—60°)–benzene gave 2,3-dihydro-5-methylquinolin-4(1*H*)-one [3] (VI), m.p. 103—104°; elution with a 55 : 45 mixture of the same solvents gave 2,3-dihydro-7-methylquinolin-4(1*H*)-one [3] (V), m.p. 108—109° [mixed m.p. with (VI), 87—92°)]. Similarly the acid (13) gave 2,3-dihydro-5,6-dimethylquinolin-4(1*H*)-one (XV), m.p. 104°, and 2,3-dihydro-6,7-dimethylquinolin-4(1*H*)-one (XIV), m.p. 135—136° (both eluted with 1 : 1 petroleum–benzene). The acid (18) gave 6,7-dichloro-2,3-dihydroquinolin-4(1*H*)-one (XX), m.p. 179—180°, and the 5,6-dichloro-isomer (XXI), m.p. 163—164° (both eluted with 1 : 1 mixture).

Acids (2) and (8) gave products from which only one of the possible isomers was isolated: 2,3-dihydro-7-methoxyquinolin-4(1*H*)-one [4] (II), m.p. 137—138° (eluted with benzene), and 7-ethoxy-2,3-dihydroquinolin-4(1*H*)-one [1] (IX), m.p. 90—91° [eluted with light petroleum (b.p. 40—60°).

The following n.m.r. spectra of the quinolones were taken at 60 MHz on a Varian spectrometer: (II), δ ($CDCl_3$), 2·48 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·33 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 3·56 (3H, s, OMe), 4·38br (1H, s, NH), 5·71 (1H, d, $J_{8,6}$ 2 Hz, 8-H), 5·91 (1H, dd, $J_{6,5}$ 8, $J_{6,8}$, 2 Hz, 6-H), and 7·29 p.p.m. (1H, d, $J_{5,6}$ 8 Hz, 5-H).

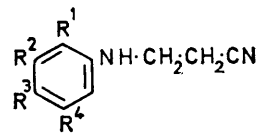
(V), δ ($CDCl_3$) 2·24 (3H, s, 7-Me), 2·61 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·52 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 4·58br (1H, s, NH), 6·46 (1H, d, $J_{8,6}$ 2 Hz, 8-H), 6·51 (1H, dd, $J_{6,5}$ 8, $J_{6,8}$ 2 Hz, 6-H), and 7·71 p.p.m. (1H, d, $J_{5,6}$ 8 Hz, 5-H).

(VI), δ ($CDCl_3$) 2·58 (3H, s, 5-Me), 2·62 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·5 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 4·58br (1H, s, NH), 6·49 (2H, dd, $J_{6,7}$ 8, $J_{8,7}$ 8, $J_{6,8}$ 2 Hz, 6- and 8-H), and 7·08 p.p.m. (1H, t, $J_{7,6} = J_{7,8} = 8$ Hz, 7-H).

(IX), δ ($CDCl_3$) 1·32 (3H, t, J 6 Hz, CH_3·CH_2), 2·48 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·35 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 3·77 (2H, q, J 6 Hz, CH_3·CH_2), 4·48br (1H, s, NH), 5·73 (1H, d, $J_{8,6}$ 2 Hz, 8-H), 5·90 (1H, dd, $J_{6,5}$ 8, $J_{6,8}$ 2 Hz, 6-H), and 7·29 p.p.m. (1H, d, $J_{5,6}$ 8 Hz, 5-H).

(XIV), δ ($CDCl_3$) 2·11 (3H, s, 6-Me), 2·15 (3H, s, 7-Me),

TABLE 1



No.	β-Anilinopropiononitriles R¹	R²	R³	R⁴	M.p. or b.p. (°C)	Crystals (solvent) *	Yield (%)	Reqd. (%) C	Reqd. (%) H	Found (%) C	Found (%) H
1	OMe	H	H	H	70—71 [a]	Yellow needles (E)	28	68·2	6·8	68·5	6·8
2	H	OMe	H	H	83—84 [b]	White needles (E)	32	68·2	6·8	68·3	6·6
3	H	H	OMe	H	60—61 [c]	White needles (A–C)	54	68·2	6·8	68·5	6·9
4	Me	H	H	H	174—178 (2·5 mmHg) [d]		25	75·0	7·5	75·3	7·6
5	H	Me	H	H	150—155 (2·0 mmHg) [e]		45	75·0	7·5	75·2	7·3
6	H	H	Me	H	102 [f]	Needles (E–F)	44	75·0	7·5	74·7	7·8
7	OEt	H	H	H	150—153 (2·0 mmHg) [g]		47	69·4	7·3	69·6	7·6
8	H	OEt	H	H	180—190 (1·0 mmHg)		53	69·4	7·3	69·3	7·3
9	H	H	OEt	H	75 [h]	White needles (E)	42	69·4	7·3	69·2	7·1
10	Me	Me	H	H	80—82 (1·0 mmHg)		59	75·8	8·4	75·7	8·2
11	Me	H	Me	H	176—177 (2·5 mmHg)		55	75·8	8·4	76·1	8·6
12	Me	H	H	Me	57—58	White leaflets (E)	35	75·8	8·4	75·6	8·3
13	H	Me	Me	H	79—80	Granules (A–C)	55	75·8	8·4	75·8	8·6
14	H	Me	H	Me	128	Needles (A–C)	59	75·8	8·4	75·7	8·5
15	Cl	Cl	H	H	140—141	Needles (A)	57	50·4	3·7	50·5	3·9
16	Cl	H	Cl	H	130—131	White needles (C)	66	50·4	3·7	50·4	3·9
17	Cl	H	H	Cl	100—101	Needles (C)	70	50·4	3·7	50·6	3·5
18	H	Cl	Cl	H	105—106	Needles (C)	72	50·4	3·7	50·3	3·7

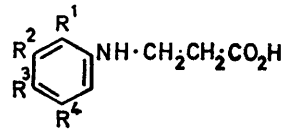
* A, Benzene; B, acetone; C, light petroleum (b.p. 40—60°); D, chloroform; E, ethanol; F, water.

[a] Lit. b.p. 165—167° at 0·6 mmHg (R. J. Bates, J. Cymerman-Craig, M. Moyle, and R. J. Young, *J. Chem. Soc.*, 1956, 388). [b] Lit. (as *a*) m. p. 84–85°. [c] Lit. (as *a*) 62—64°. [d] Lit. (as *a*) b.p. 120—121° at 0·7 mmHg. [e] Lit. (as *a*) m.p. 47—49°. [f] Lit. m.p. 104° (A. F. Bekhli, *Doklady Akad. Nauk S.S.S.R.*, 1957, **113**, 588). [g] Lit. b.p. 141—143° at 1·0 mmHg (S. A. Heininger, *J. Org. Chem.*, 1957, **22**, 1213). [h] Lit. (as *a*) m.p. 75—76°.

[3] G. R. Clemo and W. H. Perkin, jun., *J. Chem. Soc.*, 1925, **127**, 2297.

[4] J. T. Braunholtz and F. G. Mann, *J. Chem. Soc.*, 1957, 4166.

TABLE 2



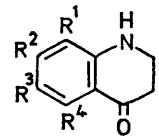
β-Anilinopropionic acids

No.	R¹	R²	R³	R⁴	M.p. (°C)	Crystals (solvent) *	Yield (%)	Required (%) C	Required (%) H	Found (%) C	Found (%) H
1 †	OMe	H	H	H	*a*	Red oil	40				
2 †	H	OMe	H	H	*b*	Red oil	31				
3 †	H	H	OMe	H	75—76 [c]	Needles (A)	22	61·5	6·6	61·4	6·6
4 †	Me	H	H	H		Brown oil	40				
5 †	H	Me	H	H		Red oil	42				
6	H	H	Me	H	82	Plates (A–C)	40	67·3	7·2	67·5	7·3
7	OEt	H	H	H	*d*	Yellow oil	31				
8	H	OEt	H	H	165—166 [e]	Needles (B–C)	20	63·1	7·1	63·0	7·1
9 †	H	H	OEt	H	106—108 [f]	Needles (A)	37	63·1	7·1	62·9	7·0
10 †	Me	Me	H	H	108—109	Needles (A–C)	40	68·2	7·7	68·3	7·6
11 †	Me	H	Me	H		Red oil	40				
12 †	Me	H	H	Me		Red oil	42				
13 †	H	Me	Me	H	91—92	Needles (A–C)	22	68·3	7·7	68·1	7·5
14 †	H	Me	H	Me		Brown oil	31				
15	Cl	Cl	H	H	144—145	Needles (G–C)	20	46·3	3·8	46·2	3·9
16	Cl	H	Cl	H	93—94	Needles (A–C)	21	46·3	3·8	46·6	3·8
17	Cl	H	H	Cl	105—106	Plates (A–C)	20	46·3	3·8	46·1	3·7
18	H	Cl	Cl	H	94—95	Needles (A–C)	40	46·3	3·8	46·2	3·7

* As in Table 1; G, ethyl acetate. † From acidic hydrolysis. Acids obtained as oils were used as such for cyclisation.

[a] Lit.,[1] m.p. 87—88°. [b] Lit.,[1] b.p. 140—145° at 0·2 mmHg. [c] Lit., m.p. 87—88°, also 76—77° (R. C. Elderfield, W. J. Gensler, T. K. Bembey, C. B. Cremer, F. Brody, K. A. Hageman, and J. D. Head, *J. Amer. Chem. Soc.*, 1946, **68**, 1259). [d] Lit.,[1] m.p. 96°. [e] Lit.,[1] b.p. 145—150° at 0·2 mmHg. [f] Lit.,[1] m.p. 104—105°.

TABLE 3



Quinolones

No.	R¹	R²	R³	R⁴	M.p. or b.p. (°C)	Crystals (solvents) *	Yield (%)	Reqd. (%) C	Reqd. (%) H	Found (%) C	Found (%) H	M.p. (°C) of DNP †	Reqd. (%) N	Found (%) N
(I)	OMe	H	H	H	220—230 (2·5 mmHg) [a]	Red oil	87	67·7	6·2	67·9	6·1	244—245	19·6	19·5
(II)	H	OMe	H	H	137—138 [b]	Prisms (E)	30	67·7	6·2	67·5	6·2	273—274	19·6	19·6
(III) §	H	H	OMe	H	111—112 [c]	Needles (A–H)	30	67·7	6·2	67·7	6·3	258—259 ‡	19·6	19·5
(IV) §	Me	H	H	H	91—92 [d]	Needles (A–C)	38	74·5	6·8	74·6	6·7	256—257 ‡	20·5	20·4
(V)	H	Me	H	H	108—109 [e]	Leaflets (H)	40	74·5	6·8	74·3	6·4	239—240	20·5	20·7
(VI)	H	H	H	Me	103—104 [f]	Needles (A–H)	20	74·5	6·8	74·6	6·7	250—251	20·5	20·4
(VII) §	H	H	Me	H	84—85 [g]	Needles (C)	37	74·5	6·8	74·6	6·9	250 ‡	20·5	20·6
(VIII) §	OEt	H	H	H	90—91 [h]	Needles (C)	74	69·1	6·8	69·0	7·0	254—255	18·8	18·6
(IX)	H	OEt	H	H	90—91 [i]	Needles (A–C)	30	69·1	6·8	69·2	6·9	252—253 ‡	18·8	18·8
(X)	H	H	OEt	H	60 [j]	Needles (A–H)	25	69·1	6·8	69·1	6·7	260—261	18·8	18·8
(XI) §	Me	Me	H	H	149—150	Needles (A–C)	74	75·4	7·5	75·3	7·5	275—276 ‡	19·7	19·6
(XII)	Me	H	Me	H	215—218 (3·0 mmHg)	Pale yellow oil	44	75·4	7·5	75·6	7·5	254—255	19·7	19·8
(XIII)	Me	H	H	Me	180—185 (2·5 mmHg)	Yellow oil	52	75·4	7·5	75·5	7·7	247—248	19·7	19·7
(XIV)	H	Me	Me	H	135—136	Needles (A–C)	38	75·4	7·5	75·3	7·5	281—282 ‡	19·7	19·4
(XV)	H	H	Me	Me	104	Plates (A–C)	15	75·4	7·5	75·6	7·6	224—225	19·7	19·8
(XVI)	H	Me	H	Me	170—175 (2·5 mmHg)	Orange oil	78	75·4	7·5	75·2	7·3	215—216	19·7	19·6
(XVII) §	Cl	Cl	H	H	153—154	Needles (A–C)	74	50·2	3·2	50·0	3·1	276—277 ‡	17·7	17·7
(XVIII) §	Cl	H	Cl	H	142—143	Needles (A–C)	66	50·2	3·2	50·3	3·4	283—284 ‡	17·7	17·7
(XIX) §	Cl	H	H	Cl	105—106	Needles (H)	61	50·2	3·2	50·1	3·2	274—275 ‡	17·7	17·5
(XX)	H	Cl	Cl	H	179—180	Leaflets (A–C)	43	50·2	3·2	50·0	3·3	293—294 ‡	17·7	17·9
(XXI)	H	H	Cl	Cl	163—164	Needles (A–C)	32	50·2	3·2	50·3	3·1	239—240 ‡	17·7	17·6

* As in Table 1; H, light petroleum. † Dinitrophenylhydrazone. ‡ Decomp. § $\lambda_{max.}$ (MeOH) values in nm (log ε) (III), 235 (4·31), 257—262 (3·87—3·83), and 380 (3·57); (IV), 232 (4·30), 255—260 (3·75), and 375 (3·63); (VII), 240 (4·28), 255—260 (3·[illegible]) and 380 (3·59); (VIII), 240 (4·22), 265—275 (3·62), and 380 (3·62); (XI), 237 (4·39), 275 (3·86), and 380 (3·67); (XVII), 2[illegible] R1), 260—270 (3·89—3·84), and 375 (3·69); (XVIII), 240 (5·02), 255—260 (3·94), and 395 (3·62); (XIX), 245 (5·07) and 375 ([illegible]e H

[a] Lit.,[1] b.p. 140—145° at 0·2 mmHg. [b] Lit.,[4] m.p. 139°. [c] Lit.,[3] m.p. 112°. [d] Lit.,[3] m.p. 92°. [e] Lit.,[3] m.p. 109°. [f] Lit.,[3] m.p. 104—105°. [g] Lit.,[3] m.p. 85—86°. [h] Lit.,[1] m.p. 144—148°. [i] Lit.,[1] b.p. 144—145° at 0·1 mmHg. [j] Lit.,[3] m.p. 60°.

2·57 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·4 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 4·35br (1H, s, NH), 6·4 (1H, s, 8-H), and 7·5 p.p.m. (1H, s, 5-H).

(XV), δ ($CHCl_3$) 2·12 (3H, s, 6-Me), 2·50 (3H, s, 5-Me), 2·61 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·21 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 4·14br (1H, s, NH), 6·15 (1H, d, $J_{8,7}$ 8 Hz, 8-H), and 6·77 p.p.m. (1H, d, $J_{7,8}$ 8 Hz, 7-H).

(XX), δ [$(CD_3)_2SO$] 2·41 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·26 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 6·57 (1H, s, 8-H), 6·68br (1H, s, NH), and 7·15 p.p.m. (1H, s, 5-H).

(XXI), δ [$(CD_3)_2SO$–$CDCl_3$] 2·4 (2H, t, $J_{2,3}$ 7 Hz, 3-H_2), 3·25 (2H, t, $J_{2,3}$ 7 Hz, 2-H_2), 6·31 (1H, d, $J_{8,7}$ 8 Hz, 8-H), 6·71br (1H, s, NH), and 6·91 p.p.m. (1H, d, $J_{7,8}$ 8 Hz, 7-H).

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