# Syntheses of 6- and 7-Carbomethoxy-1-azadecalins and 6- and 7-Carbomethoxy-1-aza-4-decalones

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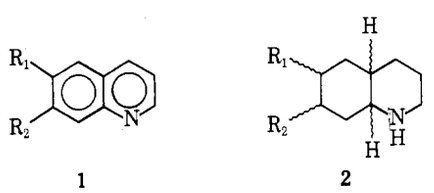
Synthetic routes to the title compounds have been investigated and all gross structures have been obtained. Problems of stereochemical assignments and epimer separations have been encountered, resulting in an inability to isolate definitive trans-fused isomers in pure form.

As part of a study of substituted *trans*-1-heteradecalins,[1] we have explored several synthetic routes to 6- and 7-carbomethoxy-1-azadecalins. Several examples of this ring system are known, with the critical reactions in their method of preparation being ring closure of nonaromatic monocyclic material,[2] Michael addition,[3] and ring closure of aromatic monocyclic material.[4] Because of our success in the 1-oxadecalin series[1] with procedures based on hydrogenation[5] of systems produced by ring closure of aromatic monocyclic material, we have pursued similar routes with the nitrogen analogs.

Initial efforts centered on hydrogenation of 6-carbomethoxyquinoline (**1a**) and 7-carbomethoxyquinoline (**1b**) in the hope that small amounts of *trans*-decahydroquinolines could be separated from the product mixture or that known reactions could be applied to the cis products to convert them into trans isomers. Quinoline-6-carboxylic acid was obtained by a modified Skraup reaction[6] on *p*-aminobenzoic acid, while quinoline-7-carboxylic acid was prepared by oxidation[7] of commercially available 7-methylquinoline. Both acids were esterified and the esters were subjected to hydrogenation at room temperature and low pressure in glacial acetic acid containing some concentrated sulfuric acid over an equal weight of Adams catalyst.[8] Good yields of mixtures of decahydroquinolines (**2a** and **2b**, respectively) were obtained.[9] In each case, glpc indicated the presence of 20% of a single isomer with a retention time shorter than that of two overlapping peaks which constituted 80% of the product mixture. Based on the behavior of the unsubstituted decahydroquinolines,[10] the earlier peak was believed to be the desired trans-fused structure.



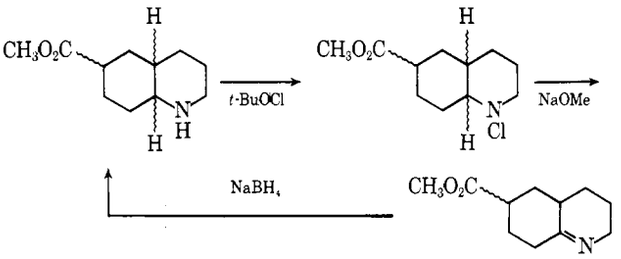
**1** **2**

**a**, $R_1 = CO_2CH_3$; $R_2 = H$
**b**, $R_1 = H$; $R_2 = CO_2CH_3$

When the mixture of 6-carbomethoxy-1-azadecalins (**2a**) was treated in a manner expected to increase the amount of trans material (Scheme I), the material with the shorter glpc retention time was enhanced to 40% of the mixture. Nevertheless, a method of separating the isomers was still required. Column chromatography on deactivated aluminas[11] permitted separation of the two pure cis isomers, but the supposed trans isomer could not be obtained in better than 50% purity. Preparative glpc was equally unrewarding since rechromatography of collected "trans material" indicated the presence of two new peaks.

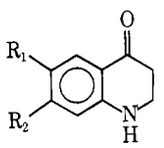
Chromatography of the mixture of 7-carbomethoxy-1-azadecalins (**2b**) on deactivated aluminas[11] resulted in pure cis isomers and a mixture containing 60% of the trans material.

**Scheme I**

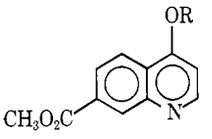



In both isomeric series (**2a** and **2b**), spectral data did not assist stereochemical assignment. The nmr (including with shift reagent), ir, and mass (including glpc–mass) spectra were all remarkably similar.

Since the above hydrogenation approach appeared unpromising, hydrogenation of 2,3-dihydro-4-quinolones along lines similar to the 4-chromanones[1,5] was investigated. Carboxylic acid **3b** was synthesized from nitroterephthalic acid with reasonable dispatch by modification of a literature method.[4] However, the decarboxylative cyclization constituting the last step in this sequence was found to be unreliable with more than 10 g of material.



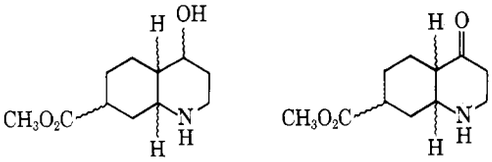
**3a**, $R_1 = CO_2H$; $R_2 = H$
**b**, $R_1 = H$; $R_2 = CO_2H$
**c**, $R_1 = CO_2CH_3$; $R_2 = H$
**d**, $R_1 = H$; $R_2 = CO_2CH_3$



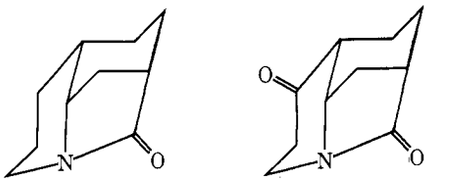
**4a**, R = H
**b**, R = $CH_3$

Conversion of acid **3b** to methyl ester **3d** using concentrated sulfuric acid as the catalyst (as reported[4] for formation of the ethyl ester) was inefficient. Attempts to increase the conversion were successful, but resulted in product of lower purity since significant amounts of quinoline **4a** were formed. Use of boron trifluoride–methanol complex[12] at reflux as the esterification reagent led to quinoline **4b** as the isolated product. Dimethylformamide dimethyl acetal[13] provided pure product **3d**, but again in low conversion. The method finally chosen involved use of a polysulfonic acid resin (Bio-Rad AGMP-50) with methanol and a Soxhlet extractor.

Hydrogenation of ester **3d** over ruthenium[5] (1.7 g catalyst/g ester) led cleanly to a decahydroquinolinol mixture (**5**) containing no aromatic material and less than 4% of benzylically hydrogenolyzed ester **2b**. Oxidation of unblocked[14] crude 7-carbomethoxy-1-aza-4-decalol (**5**) with Jones reagent[15] resulted in a low yield of a mixture con-



5 6

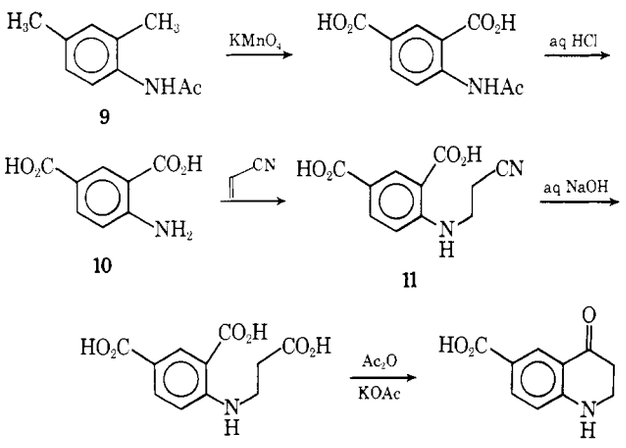


7 8

taining four isomeric ketones (6) and two lactams (7 and 8), lactam 7 evidently resulting from ring closure of hydrogenolyzed material[16] **2b** and lactam 8 from ring closure of one isomer of ketone **6**. Glpc–mass spectroscopy confirmed the structures of all of these products, but no information was obtained pertinent to stereochemical assignments in the ketone isomers, none of which were obtained in pure form.

Carboxylic acid **3a**, an unknown compound, was prepared in three ways. Application of a decarboxylative cyclization procedure[4] (Scheme II) analogous to that used

**Scheme II**

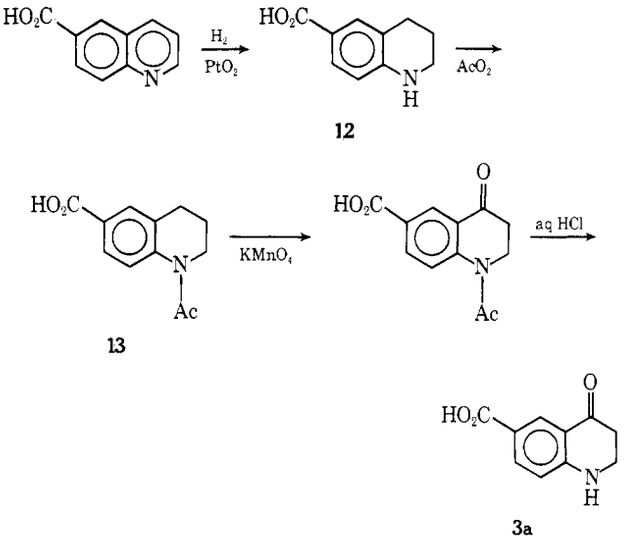


for **3b** produced the desired product in 29% yield from blocked xylidine **9**. The Michael addition (**10** → **11**) provided some difficulty, as a maximum 50% conversion could be obtained. However, repetitive additions of base and acrylonitrile to the reaction mixture produced repetitive 50% conversions so that good yields could be achieved. Use of $\beta$-propiolactone[17] instead of acrylonitrile was unsuccessful.

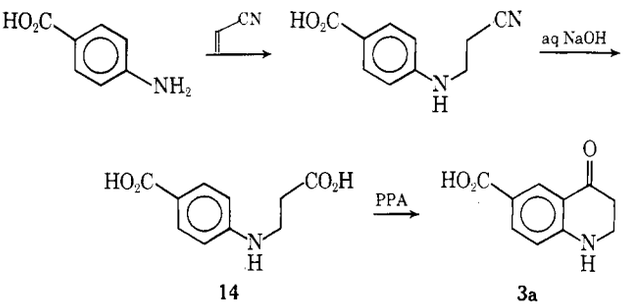
A second route (Scheme III) to acid **3a** utilized tetrahydroquinoline **12**, which could be obtained[9] from quinoline-6-carboxylic acid. Buffered permanganate oxidation[16] of blocked tetrahydroquinoline **13** proceeded satisfactorily at the benzylic position to provide acid **3a** in 37% yield from quinoline-6-carboxylic acid.

A third route, the ultimate method of choice because of its simplicity, involved intramolecular cyclization of a $\beta$-anilinopropionic acid (**14**) (Scheme IV) in a manner analogous to that used in the oxygen series.[1,5] Michael addition of *p*-aminobenzoic acid to acrylonitrile followed by hydrolysis produced acid **14**. After unsuccessful cyclization of **14** with hot sulfuric acid and of acetylated **14** with polyphosphoric acid, a technique[18] using hot polyphosphoric acid on **14** was found to give usable yields of **3a**, the overall yield for this synthetic route being 37%.

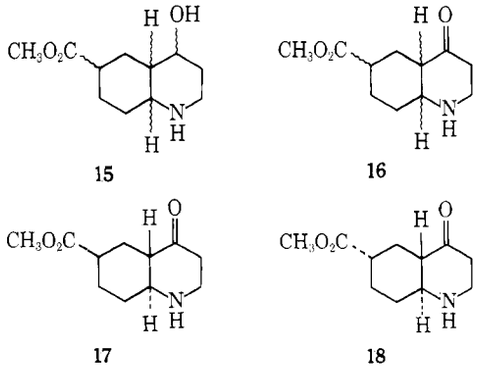
**Scheme III**



**Scheme IV**



Conversion of acid **3a** to methyl ester **3c** was achieved using the dimethylformamide dimethyl acetal method.[13,19] Hydrogenation of ester **3c** over ruthenium produced a decahydroquinolinol mixture (**15**) containing no more than 6% of hydrogenolyzed ester **2a**. Jones oxidation[15] gave a low yield of ketone mixture **16**. Column chromatography permitted separation of two fractions each containing better than 90% of the same two ketone isomers, but in different proportions (4:1 and 1:4). Equilibration[1] of these two mixtures with 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) produced no change in either the pmr spectra or the thin layer chromatograms, suggesting that these isomers were trans fused[20] (**17** and **18**) and that equilibration had occurred earlier in the sequence,[21] presumably during the Jones oxidation. Unfortunately, the spectral data provided no stereochemical information.



15 16



17 18

## Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60A instrument using solutions in deuteriochloroform unless otherwise stated. Hexadeuterated dimethyl sulfoxide was

used where DMSO is specified. Infrared spectra were determined with a Beckman IR-10 spectrophotometer, with only major absorptions being cited. Mass spectral analyses were obtained at 70 eV. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach, West Germany. The glpc column used was a 6 ft × 0.25 in. 10% *m*-polyphenyl ether (five rings) w/w on an Anakrom ABS (60/70 mesh) column.

**6-Carbomethoxyquinoline (1a).** Quinoline-6-carboxylic acid was prepared from *p*-aminobenzoic acid in 83% yield by the method of Cohn[6] and was obtained from methanol as a buff solid, mp 291–295° (lit.[22] mp 290–291°). Conversion to the methyl ester, a white solid, was effected in 61% yield by the method of Haug and Fürst,[23] mp 86–88° (lit.[24] mp 86–87°).

**7-Carbomethoxyquinoline (1b).** Quinoline-7-carboxylic acid was prepared from 7-methylquinoline in 37% yield by the method of Siebert and coworkers,[7] mp 250–255° (lit.[7] mp 252–254°). Conversion to the methyl ester was effected in 57% yield by the method of Haug and Fürst,[23] giving a white solid, mp 73–76° (lit.[24] mp 73.5–74.5°).

**6-Carbomethoxy-1-azadecalin (2a).** A solution of 1.00 g (5.34 mmol) of **1a** in 10 ml of glacial acetic acid containing 5 drops of concentrated $H_2SO_4$ was hydrogenated for 1–2 hr at 10–50 psig at room temperature over 1.00 g of $PtO_2$. Hydrogen uptake was *ca.* 6 equiv (the catalyst was not prereduced). The mixture was diluted with $CH_2Cl_2$ and the catalyst was removed by filtration. The filtrate was treated with 10 ml of 19 *N* NaOH in the cold and extracted with $CH_2Cl_2$. The extracts were concentrated, giving 1.06 g (100%) of the epimers of **2a**, glpc retention times (175°) 13.6, 17.4, and 18.3 min (1:2:2).

*Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.82; H, 9.53; N, 7.10.

Chromatography on neutral alumina (Woelm, activity grade III) of 500 mg of this epimer mixture gave 160 mg (32%) of a single cis isomer as an oil in the 50% ethyl acetate–methylene chloride fractions: ir (neat) 1745 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (13), 166 (11), 138 (7), 110 (3), 96 (100), 83 (33); glpc retention time (175°) 18.3 min.

The 5–10% methanol–ethyl acetate fractions contained 240 mg (48%) of a mixture of the other cis isomer and a trans isomer of **2a**. Chromatography on neutral alumina (Woelm, activity grade V) of this new mixture gave 30 mg (6%) of the cis isomer in the 60% benzene–heptane fractions as a white solid: ir (Nujol) 1745 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (8), 166 (7), 138 (2), 110 (2), 96 (100), 83 (17); glpc retention time (175°) 17.4 min.

The 80–90% benzene–heptane fractions contained 30 mg (6%) of a mixture of this cis isomer and the trans isomer, glpc retention times (175°) 13.6 and 17.4 min (1:1).

**7-Carbomethoxy-1-azadecalin (2b).** This compound was prepared from **1b** in 99% yield by the method used for **2a**, glpc retention times (169°) 13.0, 15.4, and 16.9 min (1:4; the latter two peaks were not well defined and were combined for this ratio).

Chromatography on neutral alumina (Woelm, activity grade IV) of 500 mg of this isomer mixture gave 200 mg (40%) of a mixture of one of the cis isomers and a trans isomer as an oil in the 0–50% methylene chloride–benzene fractions, glpc retention times (169°) 13.0 and 16.9 min.

One 50% ethyl acetate–methylene chloride fraction contained 50 mg (10%) of the other cis isomer as an oil: ir (neat) 3440 (N–H) and 1750 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (10), 166 (4), 138 (7), 110 (3), 96 (100), 83 (8); glpc retention time (169°) 15.4 min.

*Anal.* Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.97; H, 9.70; N, 7.04.

Chromatography on neutral alumina (Woelm, activity grade III) of the previously mentioned 200 mg of isomer mixture gave 40 mg (8%) of a pure cis epimer in the $CH_2Cl_2$ fractions as an oil: ir (neat) 1750 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 197 (13), 166 (7), 138 (5), 110 (6), 96 (100), 83 (10); glpc retention time (169°) 16.9 min.

The 10% methanol–ethyl acetate fractions contained 20 mg of a mixture of the latter cis isomer and the trans isomer, glpc retention times (169°) 13.0 and 16.9 min (3:2). The mass spectrum of the pure trans isomer of **2b** was recorded using gas chromatography–mass spectra: *m/e* (rel intensity) 197 (10), 110 (10), 96 (100).

**Partial Isomerization of 6-Carbomethoxy-1-azadecalin (2a).** A stirred solution of 207 mg (1.05 mmol) of isomer mixture **2a** in 2 ml of dry ether was treated dropwise with a solution of 120 mg (1.1 mmol) of *tert*-butyl hypochlorite in 2 ml of dry ether over 5 min in an ice bath. Stirring was continued in the cold for 30 min, and the resulting solution of 6-carbomethoxy-1-aza-1-chlorodecalin was then treated dropwise with a solution of 62 mg (1.1 mmol) of $NaOCH_3$ in 4 ml of dry methanol over a few minutes. Most of the ether was removed, and the solution was then refluxed for 30 min. The resulting solution was cooled and treated with 200 mg (5.3 mmol) of $NaBH_4$ and 1 drop of water. The mixture was stirred for a few minutes at room temperature, then kept at 5° for 22 hr. The mixture was treated with 1 ml of glacial acetic acid and concentrated. The residue was treated with ice and 2.5 *N* NaOH, then extracted with $CHCl_3$. The $CHCl_3$ extract was dried ($NaSO_4$) and the solvent was evaporated, giving 130 mg (63%) of a crude mixture, glpc retention times (175°) 13.6, 17.4, and 18.3 min (4:3:3).

**7-Carbomethoxy-2,3-dihydro-4(1*H*)-quinolone (3d).** A stirred mixture of 3.56 g (18.7 mmol) of **3b**[4] and 11.4 g (56 mmol) of Bio-Rad AGMP-50 (50–100 mesh granular, $H^+$ form, 52–56% moisture content) in 400 ml of methanol was refluxed through a Soxhlet extractor containing 3A molecular sieves for 49 hr. The cooled mixture was filtered and the resin was washed with methanol. The filtrate and extracts were concentrated and the residue was dissolved in $CH_2Cl_2$. The solution was washed with 5% aqueous $NaHCO_3$ and brine, and then dried ($NaSO_4$). Concentration gave 2.02 g (53%) of crude **3d**, which was purified by a single recrystallization from methanol: mp 142–143°; ir (Nujol) 3380 (N–H), 1730, and 1660 $cm^{-1}$ (C=O); nmr $\delta$ 7.89 (d, 1, $J$ = 8 Hz, H-5), 7.40 (m, 1, H-8), 7.35 (m, 1, H-6), 4.91 (broad s, 1, NH), 3.90 (s, 3, $OCH_3$), 3.62 (t, 2, $J$ = 7 Hz, $NHCH_2CH_2$), 2.72 (t, 2, $J$ = 7 Hz, $CH_2CH_2C$=O).

*Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.26; H, 5.45; N, 7.00.

**Hydrogenation of 3d.** The standard procedure[5] was used for the hydrogenation of 410 mg (2.0 mmol) of **3d** over 700 mg of 5% Ru/C. Since the product had considerable water solubility, the aqueous methanol concentration residue was treated with a small amount of brine and extracted several times with $CH_2Cl_2$. The extracts were dried ($NaSO_4$) and evaporated, giving 190 mg (45%) of a mixture of isomers of **5** as an oil (additional **5** could be obtained by ethyl acetate extraction of the brine solution): ir ($CHCl_3$) 3390 [O(N)–H] and 1743 $cm^{-1}$ (C=O); nmr $\delta$ 3.65 (s, $OCH_3$), 3.66 (s, $OCH_3$); mass spectrum *m/e* (rel intensity) 213 (10), 197 (5), 195 (14), 182 (12), 154 (13), 126 (10), 112 (100), 98 (24), 96 (71).

*Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.56. Found: C, 62.03; H, 9.00; N, 6.71.

Alternatively the aqueous methanol filtrate from the hydrogenation was simply concentrated under vacuum until most of the water had been removed. This procedure gave 72% of a solid that appeared to be an hygroscopic hydrate of **5**, but which had a comparable pmr.

**7-Carbomethoxy-1-aza-4-decalone (6). Method A.** A stirred solution of 180 mg (0.84 mmol) of epimer mixture **5** in 4 ml of acetone was treated sequentially with 0.35 ml of $H_2O$, 0.07 ml (1.3 mmol) of $H_2SO_4$, and 0.39 ml (1.1 mmol) of Jones reagent[15] (2.8 *M*) in an ice bath. After being stirred in an ice bath for 5 hr, the mixture was treated with isopropyl alcohol, and then with excess $K_2CO_3$ and brine. The mixture was extracted with $CH_2Cl_2$ several times and the organic extracts were dried ($Na_2SO_4$). Concentration of the extracts gave 130 mg of a crude oil. Chromatography on activity grade III alumina (Woelm) using $CH_2Cl_2$ gave 40 mg (*ca.* 20%) of a mixture of isomers **6** and lactam **7**. This mixture was resolved by gas chromatography–mass spectra: mass spectrum *m/e* (rel intensity) first isomer of **6** 211 (8), 180 (3), 152 (3), 124 (3), 110 (100), 97 (11); second isomer of **6** 211 (8), 180 (3), 152 (3), 124 (3), 110 (100), 97 (8); third isomer of **6** 211 (24), 180 (24), 152 (24), 124 (100), 110 (50), 97 (10); fourth isomer of **6** 211 (13), 180 (11), 152 (16), 124 (100), 110 (67), 97 (10); lactam **7** 165 (100), 137 (24), 94 (72), 80 (51), 67 (45).

**Method B.** A stirred mixture of 830 mg (3.9 mmol) of **5** hydrate and 20 ml of acetone was treated sequentially with 1.1 ml of $H_2O$, 0.22 ml (3.9 mmol) of concentrated $H_2SO_4$, and 2.8 ml (7.8 mmol) of Jones reagent[15] (2.8 *M*) in an ice bath. The ice bath was removed and stirring was continued for 2 hr. The mixture was treated with isopropyl alcohol followed by excess $NaHCO_3$. This mixture was concentrated at room temperature and the solid residue was extracted with $CH_2Cl_2$. The remaining solid was slurried with aqueous $K_2CO_3$ and further extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated, giving 860 mg of a crude oil. Chromatography on neutral alumina (Woelm, activity grade III) gave substantial amounts of an unidentified, volatile oil in the benzene fractions. The early $CH_2Cl_2$ fractions contained 60 mg of a mixture of **7**, **8**, and one isomer of **6**. The mixture was resolved by gas chromatography–mass spec-

tra. Lactam 7 exhibited the previously described mass spectrum (method A). Keto lactam 8 had mass spectrum *m/e* (rel intensity) 179 (100), 151 (20), 115 (25), 101 (65), 99 (54). The 6 present was either the first or the second isomer by mass spectrum (see method A).

The later $CH_2Cl_2$ fractions contained 50 mg (6%) of a mixture of two isomers of 6 (the third and fourth isomers): ir (neat) 1730 and 1710 $cm^{-1}$ (C=O); nmr ($CDCl_3$) $\delta$ 3.68 (s, $OCH_3$).

**4-Aminoisophthalic Acid (10).** A stirred mixture of 30 g (0.18 mol) and 2′,4′-acetoxylidide[25] (9) and 1.5 l. of water was treated portionwise with 175 g (1.10 mol) of $KMnO_4$ over 7 hr at 80–85°. After the $KMnO_4$ had been consumed, the mixture was filtered hot. The cooled filtrate was made strongly acidic with concentrated HCl and the precipitated 4-acetylaminoisophthalic acid was washed with water. The crude moist solid was treated with 300 ml of concentrated HCl and 200 ml of ethanol and heated on a steam bath for 3.5 hr. The solution was filtered hot and the filtrate was treated with saturated sodium acetate solution to pH 3–4. The precipitated solid was aged and washed with water, giving 23.6 g (72% from 9) of a solid: ir (Nujol) 3520, 3480, 3400, 3360 (N–H), 1690, and 1635 $cm^{-1}$ (C=O); nmr (DMSO-$CDCl_3$) $\delta$ 8.85 [broad s, O(N)H], 8.54 (d, $J$ = 2 Hz, H-2), 7.84 (dd, $J$ = 2, 9 Hz, H-6), 6.84 (d, $J$ = 9 Hz, H-5).

**4-[(2-Cyanoethyl)amino]isophthalic Acid (11).** A hot, stirred suspension of 13.1 g (72.4 mmol) of 10 and 2.95 g (73.6 mmol) of NaOH in 145 ml of water was treated with 9.6 ml (140 mmol) of acrylonitrile and refluxed on a steam bath for 18 hr. This mixture was further treated with 1.43 g (35.5 mmol) of NaOH and 4.8 ml (72 mmol) of acrylonitrile and heated for an additional 24 hr. This solution was stirred in an ice bath and acidified to pH *ca.* 4 with glacial acetic acid. The precipitated solid was washed with water and dried. Recrystallization from methanol gave 10.2 g (60%) of white crystals: mp 254° dec; ir (Nujol) 3360 (N–H), 2280 (C≡N), and 1680 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 9.36 [broad s, O(N)H], 8.51 (d, $J$ = 2 Hz, H-2), 7.93 (dd, $J$ = 2, 9 Hz, H-6), 6.94 (d, $J$ = 9 Hz, H-5), 3.67 (m, $NHCH_2CH_2$), 2.86 (t, $J$ = 6 Hz, $CH_2CH_2CN$).

*Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.40; H, 4.30; N, 11.96. Found: C, 56.26; H, 4.49; N, 11.90.

**4-[(2-Carboxyethyl)amino]isophthalic Acid.** A solution of 10 g (42 mmol) of 11 in 200 ml of 2.5 *N* NaOH was refluxed for 4 hr. The cooled solution was filtered and the filtrate was acidified to pH *ca.* 3 with concentrated HCl. The precipitated solid was washed with water, giving 11.1 g (100%) of a white solid: ir (Nujol) 1690 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 10.3 [broad s, O(N)H], 8.58 (d, $J$ = 2 Hz, H-2), 8.00 (dd, 1, $J$ = 2, 9 Hz, H-6), 6.89 (d, 1, $J$ = 9 Hz, H-5), 3.58 (m, 2, $NHCH_2CH_2$), 2.66 (t, $J$ = 6 Hz, $CH_2CH_2CO_2H$).

**1-Acetyl-6-carboxy-1,2,3,4-tetrahydroquinoline (13).** A mixture of 7.00 g (40.5 mmol) of quinoline-6-carboxylic acid (see 1a) and 45 ml of glacial acetic acid was hydrogenated for 55 min at 5–48 psig at room temperature using 560 mg of $PtO_2$. The catalyst was removed by filtration and the filtrate was concentrated, giving crude tetrahydro compound 12. A solution of crude 12 in 45 ml of acetic anhydride was heated on a steam bath for 1 hr. The cooled solution was treated with water and aged. The aqueous phase was decanted and the residual oil and solid were dissolved in $CH_2Cl_2$. The $CH_2Cl_2$ extract was washed with water, dried ($MgSO_4$), and concentrated, giving 5.6 g of a crude solid. The solid was washed with ether, giving 4.95 g (56% from quinoline-6-carboxylic acid) of a solid: mp 176–179° (lit.[26] mp 187°); ir (Nujol) 2640 (O–H), 1715, and 1640 $cm^{-1}$ (C=O); nmr (DMSO-$CDCl_3$) $\delta$ 7.71 (m, 2, H-5 and H-7), 7.54 (d, 1, $J$ = 9 Hz, H-8), 3.73 (t, 2, $J$ = 6.5 Hz, H-2), 2.76 (t, 2, $J$ = 6.5 Hz, H-4), 2.22 (s, 3, $COCH_3$), 2.08 (quintet, 2, $J$ = 6.5 Hz, H-3).

**1-Acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone.** A stirred solution of 2.19 g (10.0 mmol) of 13, 450 mg (11 mmol) of NaOH, and 7.20 g (60.0 mmol) of anhydrous $MgSO_4$ in 90 ml of water was treated with a solution of 3.16 g (20.0 mmol) of $KMnO_4$ in 180 ml of water at *ca.* 10°. After 5 min the ice bath was removed and stirring was continued for 20 hr. The solution was further treated with 1.0 g (6.4 mmol) of solid $KMnO_4$ portionwise over 2.5 hr and stirred for another 12 hr. The mixture was filtered and the filtrate was acidified to *ca.* pH 2 with concentrated HCl. The resulting turbid solution was saturated with NaCl and extracted with ethyl acetate. The ethyl acetate extracts were dried ($MgSO_4$) and concentrated, giving 1.85 g (79%) of crude 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone: nmr (DMSO) $\delta$ 8.45 (d, $J$ = 2 Hz, H-5), 8.13 (dd, $J$ = 2, 8.5 Hz, H-7), 7.90 (d, $J$ = 8.5 Hz, H-8), 4.21 (t, $J$ = 6 Hz, H-2), 2.86 (t, $J$ = 6 Hz, H-3), 2.38 (s, $COCH_3$).

**4-[(2-Carboxyethyl)amino]benzoic Acid (14).** A hot solution of 15 g (0.11 mol) of *p*-aminobenzoic acid and 4.2 g (0.10 mol) of NaOH in 150 ml of water was treated with 7.8 ml (0.18 mol) of acrylonitrile and refluxed on a steam bath for 20 hr. This solution was stirred in an ice bath and acidified to pH *ca.* 4 with glacial acetic acid. The precipitated solid was washed with water. A solution of this moist nitrile and 30 g of NaOH in 300 ml of water was refluxed for 4 hr. The solution was filtered, cooled, and acidified to pH *ca.* 3 with concentrated HCl. The precipitated solid was washed with water and recrystallized from aqueous methanol, giving 15.4 g (67%) of white crystals: mp 206° dec (lit.[27] mp 206–207° dec); ir (Nujol) 1685 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 7.68 (d, $J$ = 9 Hz, H-2 and H-6), 6.58 (d, $J$ = 9 Hz, H-3 and H-5), 6.33 [broad s, O(N)H], 3.32 (t, $J$ = 7 Hz, $NHCH_2CH_2$), 2.50 (t, $J$ = 7 Hz, $CH_2CH_2CO_2H$).

**6-Carboxy-2,3-dihydro-4(1*H*)-quinolone (3a). From 1-Acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone.** A mixture of 1.85 g (7.94 mmol) of 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone in 18 ml of 6 *N* HCl was heated on a steam bath for 1 hr. This suspension was cooled in an ice bath and neutralized to *ca.* pH 3 with 19 *N* NaOH. The precipitated solid was washed with water, giving 1.27 g (84%) of a solid: ir (Nujol) 3380 (N–H) and 1675 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 8.26 (d, $J$ = 2 Hz, H-5), 7.83 (dd, $J$ = 2, 8.5 Hz, H-7), 7.51 (broad s, NH), 6.85 (d, $J$ = 8.5 Hz, H-8), 3.56 (t, $J$ = 7 Hz, H-2), 2.62 (t, $J$ = 7 Hz, H-3).

**From 4-[(2-Carboxyethyl)amino]isophthalic Acid.** The desired compound was prepared from 4-[(2-carboxyethyl)amino]isophthalic acid in 65% yield by the method used for 3b.[4] The nmr spectrum was as previously described.

**From 14.** A mixture of 1.00 g (4.79 mmol) of 14 and 10.8 g of polyphosphoric acid was heated on a steam bath for 20 hr. The cooled solution was treated with ice, and the solid which gradually separated was washed with water, giving 510 mg (56%) of 3a; ir spectrum was as previously described.

**6-Carbomethoxy-2,3-dihydro-4(1*H*)-quinolone (3c).** A mixture of 5.04 g (37.9 mmol) of 3a, 9.0 ml (*ca.* 2 equiv) of dimethylformamide dimethyl acetal,[13] and 25 ml of DMF was stirred at room temperature for 20 hr. This solution was diluted with 5% aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were washed with brine, dried ($Na_2SO_4$), and concentrated. The residue was pumped at 70–80° under vacuum to remove DMF. The remaining residue was recrystallized from methanol, giving 1.13 g (20%) of yellow-brown crystals: mp 157–158°; ir (Nujol) 3395 (N–H), 1725, and 1665 $cm^{-1}$ (C=O); nmr (DMSO) $\delta$ 8.21 (d, 1, $J$ = 2 Hz, H-5), 7.79 (dd, 1, $J$ = 2 and 9 Hz, H-7), 7.55 (broad s, 1, NH), 6.83 (d, 1, $J$ = 9 Hz, H-8), 3.80 (s, $OCH_3$), 3.56 (dt, $J$ = 2 and 7 Hz, $NHCH_2CH_2$), 2.60 (t, $J$ = 7 Hz, $CH_2CH_2C$=O).

*Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.25; H, 5.40; N, 7.00.

**Hydrogenation of 3c.** The standard procedure[5] was used for the hydrogenation of 1.10 g (5.36 mmol) of 3c over 1.9 g of 5% Ru/C. Since the product had no great water solubility, the aqueous methanol concentration residue was simply extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated, giving 530 mg (46%) of a mixture of isomers 15 as an oil: ir (neat) 3330 [O(N)–H] and 1740 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$).

*Anal.* Calcd for $C_{11}H_{19}NO_3$: C, 61.93; H, 8.98; N, 6.56. Found: C, 62.19; H, 9.01; N, 6.46.

**6-Carbomethoxy-1-aza-4-decalone (16).** This isomer mixture was prepared from isomer mixture 15 by method A used for 6. Chromatography of the 590 mg of crude 16 obtained on neutral alumina (Woelm, activity grade III) gave an unidentified volatile oil in the benzene fractions. The 90% $CH_2Cl_2$–benzene fractions contained 50 mg (10%) of a mixture of 17 and 18 as an oil: nmr $\delta$ 3.68 (s, $OCH_3$); tlc (silica gel, 8:2:1 heptane–EtOAc–diethylamine) $R_f$ minor 0.14, major 0.20, unknown 0.29.

The $CH_2Cl_2$ fractions contained 70 mg (14%) of a mixture of 17 and 18 as a low-melting solid: ir (Nujol) 3400 (N–H) and 1730 $cm^{-1}$ (C=O); nmr $\delta$ 3.67 (s, $OCH_3$); tlc (silica gel as above) $R_f$ major 0.14, minor 0.20; gas chromatography–mass spectra *m/e* (rel intensity) major 211 (12), 180 (17), 152 (17), 124 (65), 110 (100), 97 (35); minor 211 (23), 180 (4), 152 (22), 124 (26), 110 (100), 97 (34).

**Attempted Equilibration of Mixtures of 17 and 18.** Equilibrations were carried out as before.[1] The DBN was removed by chromatography on neutral alumina (Woelm, activity grade III) using $CH_2Cl_2$.

Application of this technique to the 50-mg sample of 17 + 18 resulted in the recovery of 40 mg (80%) of material that showed

no change in nmr or tlc from that of the starting mixture. Gas chromatography–mass spectra of the recovered material: *m/e* (rel intensity) major identical with that of the minor component of the 70-mg sample; minor 211 (15), 180 (15), 152 (9), 124 (26), 110 (100), 97 (31).[28]

Application of this technique to the 70-mg sample of **17** + **18** likewise resulted in no change in tlc.

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**Registry No.**—**1a,** 38896-30-9; **1b,** 51552-68-2; **2a** cis epimer 1, 51552-69-3; **2a** cis epimer 2, 51552-70-6; **2a** trans epimer, 51552-71-7; **2b** cis epimer 1, 51552-72-8; **2b** cis epimer 2, 51552-73-9; **2b** trans epimer, 51552-74-0; **3a,** 51552-75-1; **3b,** 19384-65-7; **3c,** 51552-76-2; **3d,** 39011-44-4; **5,** 51552-77-3; 6 isomer 1, 51552-78-4; 6 isomer 2, 51552-79-5; 6 isomer 3, 51552-80-8; 6 isomer 4, 51552-81-9; **7,** 51552-82-0; **8,** 51552-83-1; **9,** 2050-43-3; **10,** 33890-03-8; **11,** 51552-84-2; **13,** 51552-85-3; **14,** 51552-86-4; **15,** 51552-87-5; **17,** 51552-88-6; **18,** 51552-89-7; 4-[(2-carboxyethyl)amino]isophthalic acid, 51552-90-0; quinoline-6-carboxylic acid, 10349-57-2; 1-acetyl-6-carboxy-2,3-dihydro-4(1*H*)-quinolone, 51552-91-1.

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# An Improved Synthesis of Indenes. II. Alkyl-Substituted Indenes[1]

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Dialkylphthalans **3,** unlike their spiro analogs, are stable to both hot formic acid and boron trifluoride etherate. Dialkyl indenes **4** (R and R′ alkyl) can, however, be prepared from diols **2** by a new procedure which involves heating the derived monoacetate **6** with hot acetic anhydride–formic acid. While this procedure is not efficient for the preparation of 3-arylindenes, the latter can be prepared in good yield from the corresponding diol **2** or phthalan **3** by use of either sulfuric acid–carbon tetrachloride (0°) or polyphosphoric acid (60°).

While fused indenes can be easily prepared[2] from spirophthalans analogous to **3,** or from the corresponding diols analogous to **2,** our initial attempts to extend this synthesis to simple acyclic indenes **4** were unsuccessful; results consistent with earlier reports.[3] We have now studied a series of acyclic diols **2** and phthalans **3** (Scheme I) and have defined useful conditions for their conversion to indenes **4.**

Phthalans **3a** and **3b** (where R = alkyl), in sharp contrast[2] to their cyclic analogs, are quite stable to hot formic acid and to hot boron trifluoride etherate in hot benzene; no evidence of decomposition or indene formation was noted. With stronger acids (PPA, $H_2SO_4$) these phthalans gave small amounts of indenes; however, higher condensation products predominate and the procedure is of no synthetic value.

It was observed that reaction of diol **2a** with hot formic acid gave **3a** and, significantly, some indene **4a** (8%). Since **3a** does not give **4a** under these conditions, it was concluded that diols **2** could be converted to indenes **4** by a process not involving phthalans **3,** and that successful conversion of **3a** to indene depended upon inhibiting path A relative to path B in Scheme II. Replacement of the primary hydroxyl group in **2** by acetoxy, as in **6** (Scheme III), was investigated since $CH_3C{=}O^+$ would be a poorer leaving group than $H^+$ which, consequently, should inhibit path A relative to path B (Scheme II). Satisfactory yields of indenes **4a** (60%) and **4b** (59%) were formed to-