determined to be 2,6-dichlorobenzaldehyde 2,4-DNP, 94.6%; 2,6-dichlorobenzaldehyde-*d* 2,4-DNP, 5.4%. The isotope effect for this reaction, with corrections as in run 9, is calculated to be 19.5.

The isotopic composition, determined *via* mass spectrometry, for 2,6-dichlorobenzaldehyde-*d* 2,4-DNP, prepared in the usual way from 2,6-dichlorobenzyl alcohol-$\alpha$-$d_2$, was >99.5% $d_1$.

The isotopic composition of the 2,6-dichlorobenzyl alcohol-$\alpha$-$d_2$ was determined by nmr *vs.* a weighed internal benzyl alcohol-O-*d* standard in chloroform-*d* solution. The dideuterated alcohol (1.02 mmol) was found to contain 0.016 mmol (1.6%) of monodeuterio alcohol (broad multiplet at $\delta$ 4.70 ppm) by comparison with 0.019 mmol of the standard (sharp singlet at $\delta$ 4.40 ppm), average of nine scans.

**Registry No.**—Manganese dioxide, 1313-13-9; benzyl alcohol, 100-51-6; 2,6-dichlorobenzyl alcohol-$\alpha$-$d_2$, 21369-49-3; benzaldehyde-$\alpha$-$d_1$ (2,4-dinitrophenylhydrazone), 21273-19-8.

**Acknowledgment.**—The technical assistance of Mrs. Nancy N. Arnold, Mr. Robert F. Mushinsky, Mr. Thomas Toolan, and Mr. Robert Hickey is gratefully acknowledged, as are the helpful suggestions of Professors Biemann, Corey, and Kemp. The preliminary mass spectra were provided by Dr. Christopher Falshaw of Professor Biemann's Laboratory.

# 9-Aza Steroids. III.[1] The Synthesis of Some 2-Cyclopentylquinolines as Models for Rings A, B, and D

J. D. BATY, GURNOS JONES, AND C. MOORE

*Department of Chemistry, University of Keele, Staffordshire ST5 5BG, England*

*Received March 6, 1969*

A number of 2-(2-quinolyl)cyclopentanones, **2**, **19**–**22**, and **24**, potential intermediates in a 9-aza steroid synthesis, have been prepared by two routes from quinoline N-oxide. The first involves reaction with the enamine of cyclopentanone; the second, condensation with a suitably activated cyclopentanone in the presence of acetic anhydride. Attempts to add a two-carbon unit bridging ring C either by condensation at the cyclopentanone carbonyl or by alkylation at the nitrogen atom have failed. The 2-(2-quinolyl)-2-carbethoxycyclopentylidenecyanoacetate (**40**) could not be reduced or cyclized to a tetracyclic derivative. Quinoline reacted with acetyl chloride and 2-substituted cyclopentanones to give either an N-acetyl-1,4-dihydroquinoline (**47**) or an N-acetyl-1,2-dihydroquinoline (**48**). The reaction failed with other acyl chlorides, giving instead the enol acetates derived from the cyclopentanones.

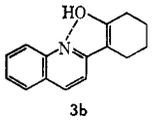
We have reported[1,2] approaches to a 9-aza steroid synthesis in which rings A, B, and C were prepared bearing substituents suitable for the elaboration of ring D (**1**). However we have had difficulty in obtaining a quantity of intermediate **1**, and lack of success in alkylation experiments on this intermediate[3] and on N-phenyl-4-piperidone, combined with variable success in the cyclization of 3-acetonyl-4-piperidones,[4] have led us to abandon this approach. We discuss here investigation of an alternative route to 9-aza steroids involving the preparation of 2-cyclopentylquinolines (representing rings A, B, and D in the final steroid).

The simplest model for our purpose was 2-(2-quinolyl)cyclopentanone (**2**); Hamana and Noda[5] have prepared 2-(2-quinolyl)cyclohexanone (**3**) from quinoline N-oxide and the morpholine enamine of cyclohexanone, in the presence of benzoyl chloride. By using the enamine of cyclopentanone under their conditions, a good yield of a compound having the correct molecular formula was obtained. However, its orange color, the absence of any absorption in the normal saturated carbonyl region of the infrared, and its nmr spectrum could be interpreted in terms of the 1,2-dihydroquinolylidenecyclopentanone (**2a**); Hamana and Noda's compound might be similarly **3a**.[6] Compound **2** failed to react with methylmagnesium iodide, as did also its hydrochloride, which is certainly in the quinoline form. Not unexpectedly, the compound **2** also failed to react under Knoevenagel conditions with malononitrile, cyanoacetic esters, or cyanoacetamide, nor could an ethylene ketal be obtained. Reduction of the compound **2a** with sodium borohydride gave 2-(2-quinolyl)cyclopentanol (**4**), which was dehydrated by distillation from potassium hydroxide to give 2-(2-quinolyl)cyclopentene (**5**). We were unable to obtain Michael addition products from the cyclopentene **5** under a variety of conditions (listed in the Experimental Section) with malonic ester, cyanoacetic esters, or *t*-butyl acetoacetate, and hence were forced to abandon this attempt to introduce the required two-carbon bridge for ring C.

As the major obstacle to further elaboration of the cyclopentanone in compound **2a** seems to involve the potential conjugation between ketone and quinoline, we have investigated the properties of 2-(2-quinolyl)-cyclopentanones in which a second 2 substituent prevents the formation of dihydroquinolylidene tautomer. An excellent route to 2-substituted quinolines is offered by the reaction between quinoline N-oxide and active methylene derivatives in acetic anhydride, reported by Hamana and Yamazaki;[7] a discussion of the structure of two such compounds (prepared by an alternative route from 2-chloroquinoline and the appropriate sodium salt) has been given by Borror and Haeberer.[8]

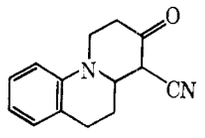
(1) Part II: G. Jones and J. Wood, *Tetrahedron*, **21**, 2961 (1965).
(2) G. Jones and J. Wood, *ibid.*, **21**, 2529 (1965).
(3) Unpublished work.
(4) M. Alam, J. D. Baty, G. Jones, and C. Moore, *J. Chem. Soc., C*, 1520 (1969).
(5) (a) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965); (b) P. Bruni and A. Strocchi, *Ann. Chim.* (Rome), **56**, 767 (1960).

(6) Hamana and Noda interpret their results in terms of the enol structure **3b**; however, 2-cyclopentenylquinoline is not colored. Note also the similarity with compound **25** described subsequently.

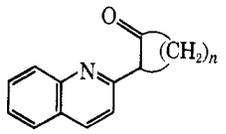



3b

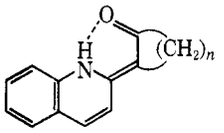
(7) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (Tokyo), **11**, 415 (1963).
(8) A. L. Borror and A. F. Haeberer, *J. Org. Chem.*, **30**, 243 (1965).



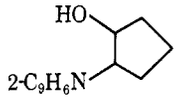
1



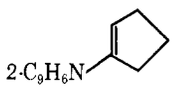
2, $n = 3$
3, $n = 4$



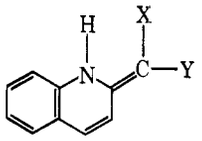
2a, $n = 3$
3a, $n = 4$



4

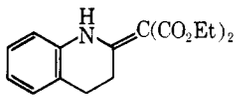


5



6, X = $CO_2Me$, Y = CN
7, X = $CO_2$-t-Bu, Y = CN
8, X = $CONH_2$, Y = CN
9, X = $COCH_3$, Y = $CO_2Et$
12, X = Y = $CO_2Et$

2-$C_9H_6N$-CR′(R″)$CO_2Et$
10, R′ = H, R″ = $CH_3$
11, R′ = R″ = H
13, R′ = $CH_3$, R″ = $COCH_3$



18

2-$C_9H_6N$-CX(Br)Y
14, X = $CO_2Me$, Y = CN
15, X = $CO_2$-t-Bu, Y = CN
16, X = $CONH_2$, Y = CN
17, X = Y = $CO_2Et$

In preliminary experiments, we obtained from quinoline N-oxide and methyl cyanoacetate the quinolylidenecyanoacetate **6**; *t*-butyl cyanoacetate gave compound **7** and cyanoacetamide **8**, the yields being 78, 65, and 90%, respectively. Our spectral details confirm the structures as preferred by Borror and Haeberer. Notably, the nmr spectra in neutral media show a broadened one-proton peak at *ca.* 13 ppm due to the NH; on the other hand, the spectra in TFA (of the protonated forms **6a–8a**) show a sharp one-proton singlet in the region 4–6 ppm due to the CH (X,Y) system. As our planned route involved 2-quinolyl β-ketonic esters, we also allowed to react quinoline N-oxide and ethyl acetoacetate, obtaining in excellent (86%) yield the quinolylideneacetoacetate **9**, the structure being again indicated by the nmr spectrum. As our first attempt to lock the compound into the true quinoline form, we treated the keto ester **9** with sodium hydride, then with methyl iodide;[9] we obtained, surprisingly, a good yield of ethyl 2-(2-quinolyl)propionate (**10**). We found that sodium hydride in slight excess was leading to an alkaline medium during work-up; in fact, under the conditions described above but omitting the methyl iodide, the keto ester **9** gave an excellent yield of ethyl 2-quinolylacetate (**11**).[10] By neutralizing the alkylation mixture with glacial acetic acid before adding water, it was possible to obtain an orange oil showing the spectral characteristics expected of the methylated keto ester **13** (carbonyl absorption at 1740 and 1690 $cm^{-1}$, nmr showing methyl singlet at 1.81 ppm), but attempts at purification, or exposure to moist air, led to rapid decomposition to a mixture of ester **10** and acetic acid. Attempts at acylation of the keto ester **9** were unsuccessful.

In a second attempt to obtain quinolyl rather than quinolylidene derivatives, we have treated the derivatives **6–8** and **12** with bromine. All reacted rapidly to give in high yield monobromo derivatives, formulated as **14–17**; as an example, the ester carbonyl stretching in the bromo derivative **14** was at 1743 $cm^{-1}$ compared with 1636 $cm^{-1}$ in the quinolylidene derivative **6**.[13] We have found that hydrogenation of the malonate **12** is very slow and proceeds only to the dihydro stage **18**. We assume this to be another example of the by now well-known stability of such enamines bearing an electron-withdrawing substituent in the β position.[14] Finally, Borror and Haeberer have reported[8] difficulty in removing the *t*-butyloxycarbonyl group from ester **7**; we have found that it is smoothly lost in warm TFA, giving 2-quinolylacetonitrile.

With this experience in the reaction between quinoline N-oxide and β-keto esters, we turned our attention again to the cyclopentyl series. Reaction with ethyl cyclopentanone-2-carboxylate gave the keto ester **19**; similar reaction with *t*-butyl cyclopentanone-2-carboxylate gave keto ester **20**. It is important to prove that the substituent has entered the 2 position on the quinoline nucleus and not the 4 position as occasionally occurs. The most obvious point in the nmr spectrum was the absence of any downfield doublet due to the quinoline 2 proton; confirmation of the 2 substitution was obtained by oxidation of keto ester **19** using peracetic acid, giving quinaldic acid N-oxide, identical with a specimen obtained by oxidation of ethyl 2-quinolylacetate (**11**). The ester **19** was readily hydrolyzed by cold dilute sodium hydroxide; the acid, obtained in 90% yield, showed in the nmr the usual 2-substituted quinoline pattern and a carboxylic acid proton at 11.5 ppm. However, the rest of the spectrum (a four-proton multiplet at 1.83, a two-proton triplet at 2.83, and a two-proton triplet at 3.06 ppm) established the compound as 5-(2-quinolyl)pentanoic acid (**21**). We have already noted the facile nucleophilic attack on keto ester **9** and we have no doubt that the retro Dieckmann reaction on ester **19** also reflects the stabilization of negative charge on the carbon atom adjacent to the 2-quinolyl position. We had expected to be able to remove the *t*-butyloxycarbonyl group at this stage or later; we were unable

(9) As the anion is ambident, we hoped also to obtain some evidence of N methylation, but no N-methyl derivative was detected.

(10) This, in our opinion, represents the simplest synthesis of ethyl 2-quinolylacetate; the published procedures, involving reaction between quinaldinyllithium and diethyl carbonate[11] or ethyl chloroformate,[12] gave yields of only 20–30% of the ester **11**. By using ethyl chloroformate in excess at −78°, we have obtained ethyl quinolylacetate (17%) and the quinolylidenemalonate **12** (18%), and partial hydrolysis and decarboxylation of the malonate gave a total yield of 33% ester **11**.

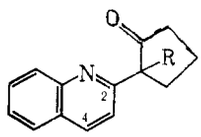
(11) D. L. Hammick, E. Johnston, and E. D. Morgan, *J. Chem. Soc.*, 2196 (1952).

(12) J. D. Kendall, H. R. J. Waddington, and G. F. Duffin, British Patent 867,592 (1961).

(13) It has been reported [K. Golankiewicz, *Rocz. Chem.*, **36**, 625 (1962)] that the quinolylidenemalonate **12** gives a pentabromo derivative. The only difference we can detect between our procedure and that of Golankiewicz is a bicarbonate basification during our work-up. It is possible that Golankiewicz's bromination product is the 1,2-dibromo-1,2-dihydroquinoline tribromide.

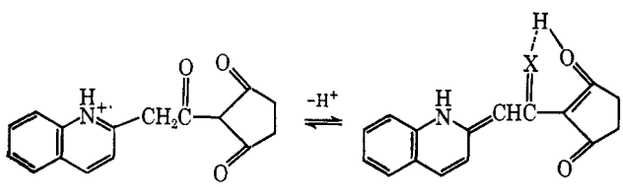
(14) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).

to remove the group from ester **20** by any of the standard procedures, and hydrolysis gave merely the pentanoic acid **21**. Reaction between quinoline N-oxide and 2-cyanocyclopentanone gave the cyano ketone **22**. This compound proved even less stable to base than the esters **19** and **20**; aqueous sodium carbonate converted the cyano ketone **22** quantitatively into the cyano pentanoic acid **23** (even moist air converted the ketone **22** to the acid **23**). The only other simple



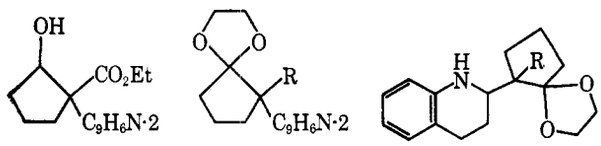
**19**, R = $CO_2Et$
**20**, R = $CO_2$-*t*-Bu
**22**, R = CN

2-$C_9H_6N$-CH(R)$CH_2CH_2CH_2CO_2H$
**21**, R = H
**23**, R = CN



**24**

**25**, X = O
**26**, X = NH



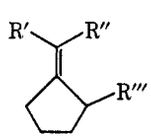
**27**



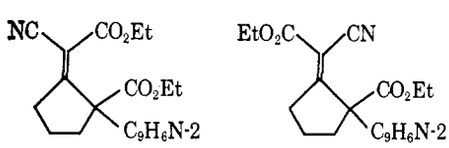
**28**, R = $CO_2Et$
**29**, R = $CO_2$-*t*-Bu



**30**, R = $CO_2Et$
**31**, R = $CO_2$-*t*-Bu



**32**, R′ = R‴ = $CO_2Et$, R″ = CN
**33**, R′ = R″ = R‴ = $CO_2Et$
**34**, R′ = R″ = R‴ = $CO_2Me$
**35**, R′ = R″ = CN, R‴ = H
**36**, R′ = CN, R″ = $CO_2Et$, R‴ = H
**37**, R′ = CN, R″ = $CO_2$-*t*-Bu, R‴ = H
**38**, R′ = R″ = $OCOC(CH_3)_2COO$, R‴ = H
**39**, R′ = R″ = $CO_2Et$, R‴ = H



**40** **41**

cyclopentane derivative which we have treated with quinoline N-oxide was 2-acetylcyclopentane-1,3-dione. The product was an orange solid, soluble in aqueous and organic bases and showing infrared absorption at 1680 and 1640–1605 $cm^{-1}$. The nmr spectrum (in TFA) showed no acetyl methyl, but, in addition to the six aromatic protons, a singlet at 3.02 ppm (4 H) and a singlet at 5.16 (2 H) indicated the structure **24**. The most likely structure for the unprotonated compound, in view of the color, is **25**. It is surprising to find that the condensation has taken place with the methyl group in preference to the much more acidic (though presumably hindered) methine.[15] An attempted reaction between the compound **25** and malononitrile in the presence of ammonium acetate gave a compound whose nmr spectrum and analysis showed it to be the imine **26**.

With the 2-(2-quinolyl)cyclopentanones **19**, **20**, and **22** available in quantity, we sought routes to introduce the two-carbon fragment necessary to bridge ring C. Attempts at Knoevenagel condensation reactions on the keto ester **19** with ethyl cyanoacetate under a variety of conditions were uniformly unsuccessful.[16] Hydrogenation of the keto ester **19** with palladium on charcoal at room temperature was slow; the product was the cyclopentanol **27** without reduction of the quinoline system. To avoid this prior reduction of the ketone during the more drastic conditions necessary to reduce the quinoline, the cyclopentanones **19** and **20** were ketalized; prolonged reaction in benzene or the use of higher temperatures failed to improve the yield of ethylene ketals **28** and **29** beyond 42% and 36% respectively, possibly because of the already mentioned instability of the keto esters **19** and **20**. Hydrogenation of the ketals **28** and **29** was slow, but yields of the tetrahydroquinolyl derivatives **30** and **31** were good. Unfortunately, all attempts at alkylation of the secondary amines **30** and **31** with acrylonitrile were unsuccessful; in view of the steric obstacles still present toward substitution on the cyclopentanone carbonyl, this route was not further pursued.

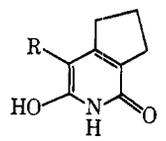
We have also made some attempts to extend the scope of Hamana and Yamazaki's synthesis by condensation of quinoline N-oxide with cyclopentylidene derivatives of the general type shown by formulas **32–39**, in which the activation is provided by vinylogous electron-withdrawing groups and in which the two-carbon chain required for ring C is already present. The cyano diester **32** reacted with quinoline N-oxide to give a very unstable orange oil; although only nitrogen analyses were consistent, the nmr spectrum leaves no doubt that the product was the desired compound **40** with its stereoisomer **41** (the splitting on the ester methylene and methyl groups indicates three different types of ester). The compound **40** lacked the 2-quinoline doublet; its six-proton aromatic multiplet could be compared with the four-proton ester methylene multiplet and the six-proton ester methyl multiplet. The cyclopentane protons showed as two groups in a ratio of 2:1. Catalytic reduction of the mixture of esters **40** and **41** was extremely slow and gave a mixture; the infrared spectra showed loss of the nitrile peak. Attempted reduction of the esters **40** and **41** by sodium borohydride in ethanol or isopropanol was also unsuccessful. Since the prior reduction of the nitrile group presented a serious obstacle, we attempted to convert the cyano diester to a triester, but all attempts at ethanolysis were unsuccessful.

As alternatives in the condensation with quinoline N-oxide, we attempted to prepare first the triester **33**.

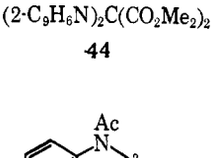
(15) Hamana and Yamazaki were unable to obtain reaction between quinoline N-oxide and acetophenone or acetone.[7]

(16) Steric hindrance to Knoevenagel condensation is severe in α,α-disubstituted cycloalkanones; see G. Jones, *Org. Reactions*, **15**, 204 (1967).

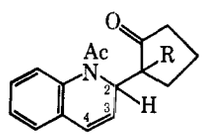
Treatment of the cyano diester **32** with ethanolic sulfuric acid gave the pyridine **42**, previously reported by Kon and Nanji.[17] With methanolic hydrogen chloride, the methyl ester **43** was obtained. Hydrolysis of cyano diester **32** with base gave a crude mixture of acids;[18] esterification gave a product shown by nmr to be predominantly the triester **34**. Reaction with quinoline N-oxide gave as the only recognizable product the diquinolyl diester **44**, identified by conversion into the known di(2-quinolyl)methane.[19] In order to determine the necessity for extra activation provided by electron-withdrawing groups $R_3$ in the cyclopentylidene derivatives, we have prepared the derivatives **35–39**.[20–22] All apparently reacted with quinoline N-oxide (the malononitrile derivative **35** violently), but no pure products could be obtained from the reaction mixtures.



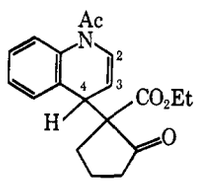
**42**, R = $CO_2Et$
**43**, R = $CO_2Me$



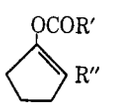
**44**



**46**, R = $CO_2Et$
**48**, R = CN



**47**



**49**, R′ = $CH_3$, R″ = CN
**50**, R′ = $CH_2Cl$, R″ = $CO_2Et$
**51**, R′ = $CH_2Cl$, R″ = CN
**52**, R′ = $CH_2OEt$, R″ = $CO_2Et$
**53**, R′ = $CH_2OEt$, R″ = CN

In a final attempt to obtain suitable 2-cyclopentylquinolines, we investigated a route reported by von Dobeneck and Gotzsche.[23] Here, quinoline reacts with active methylene derivatives in the presence of acyl halides to give N-acyl-1,2-dihydroquinolines. The reaction using acetyl chloride and 2-carbethoxycyclopentanone was slow, but after 3 days we obtained a crystalline compound in 40% yield, having the correct analytical composition for **46**. However, the nmr spectrum showed single-proton absorptions at 4.52 (doublet, $J$ = 6 Hz), 5.62 (overlapping doublets, $J$ = 6 and 7 Hz), and 7.08 ppm (doublet, $J$ = 7 Hz), which are better fitted to the 1,4-dihydroquinoline structure **47** (protons 4, 3, and 2, respectively). A deshielded proton at 8.05 ppm ($J$ = 6 and 2 Hz) is probably proton 5, deshielded by the cyclopentanonecarboxylate, since it has been reported[24] that, in N-acyl-1,2,3,4-tetrahydroquinolines, the acyl group is oriented away from the benzene ring and does not deshield proton 8. By contrast with this result, the reaction between quinoline, acetyl chloride, and 2-cyanocyclopentanone was rapid and exothermic, and the only solid product was shown by its nmr spectrum to be 1-acetyl-2-(2-cyano-2-cyclopentanonyl)-1,2-dihydroquinoline (**48**). The single-proton signals are now at 5.65 (doublet, proton 2), 6.38 (quartet, proton 3), and 7.0 ppm (doublet, proton 4), with $J_{2,3}$ = 6 Hz and $J_{3,4}$ = 10 Hz, in good agreement with the expected figures for a styrene derivative; as anticipated, there is now no deshielded proton beyond the main aromatic peak at 7.3 ppm. An attempt to cause an intramolecular cyclization of amide **48** using sodium hydride was unsuccessful.

A second (liquid) product from the reaction which gave compound **48** was shown by analysis and nmr spectrum to be 1-acetoxy-2-cyanocyclopentene (**49**). Attempts to use other acyl chlorides in the reaction between quinoline and cyclopentanones gave as the only isolated products the appropriate enol acetates of the starting cyclopentanones. Thus, chloroacetyl chloride gave with 2-carbethoxycyclopentanone the chloroacetoxycyclopentene **50** and with 2-cyanocyclopentanone the derivative **51**, and ethoxyacetyl chloride gave the enol acetates **52** and **53**. In none of these reactions was any N-acyldihydroquinoline obtained, and the quinoline appears to function purely as a basic catalyst; the yields varied from 50% for compound **51** up to 92% for compound **53**. Under the same conditions, cyanoacetyl chloride, quinoline, and 2-carbethoxycyclopentanone gave an inseparable mixture of products.

## Experimental Section

**2-(2-Quinolyl)cyclopentanone** (**2**) was prepared as described by Hamana and Noda,[5a] using the morpholine enamine of cyclopentanone. The orange-red 2-quinolylcyclopentanone **2** had mp 99–101° (from petrol, bp 60–80°) (82%); ir $\nu_{max}^{Nujol}$ 1660 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 2.0 (m, 2), 2.5 (m, 4, cyclopentane), 6.6 (d, 1, quinoline 3 H, $J$ = 10.5 Hz), and 7.1–7.8 (m, 5, aromatic H). The hydrochloride, recrystallized from EtOH–ether, had mp 168–170°.

*Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2; N, 6.65. Found: C, 79.3; H, 6.4; N, 6.45.

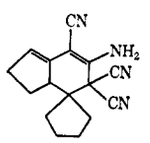
Attempts to prepare an ethylene ketal by boiling the cyclopentanone **2** with ethylene glycol in boiling benzene with toluene *p*-sulfonic acid failed; Knoevenagel condensations using methyl

(17) G. A. R. Kon and H. R. Nanji, *J. Chem. Soc.*, 2429 (1932).

(18) I. Vogel, *ibid.*, 2018 (1928).

(19) Hamana and Yamazaki (ref 7) obtained a small yield of the corresponding diethyl malonate from the reaction between quinoline N-oxide and diethyl malonate, and it seems reasonable to suppose that the ester **44** is the product from quinoline N-oxide and dimethyl malonate, formed by a retro Knoevenagel condensation (the reaction was slow, *ca.* 16 hr).

(20) Extreme care is necessary in the condensation of cyclopentanone with malononitrile, or the product is a dimer, formulated as **45** by analogy with that obtained from cyclohexanone [M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, **42**, 1440 (1964)].



**45**

(21) Compound **37** was rather surprisingly obtained when 2-carbomethoxycyclopentanone and *t*-butyl cyanoacetate were heated in xylene with piperidine.

(22) Compound **39** is obtained when the isopropylidene derivative **38** is treated with ethanolic hydrogen chloride.

(23) H. von Dobeneck and W. Gotzsche, *Chem. Ber.*, **95**, 1484 (1962).

(24) K. Nagarajan, M. O. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967); however, M. J. Sewell and A. M. Munro have thrown some doubt on this suggestion [*Tetrahedron Lett.*, 595 (1969)].

or ethyl cyanoacetate, malononitrile, or cyanoacetamide gave no condensation products.

**2-(2-Quinolyl)cyclopentanol (4).**—The cyclopentanone **2** (3 g) reduced with $NaBH_4$ (0.5 g) in EtOH gave the cyclopentanol **4** from benzene: mp 97–98°; yield 2.9 g (96%); ir $\nu_{max}^{CHCl_3}$ 3550 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.6–2.6 (m, 5, cyclopentane H + OH), 3.0–3.6 (m, 1, quinoline CH), 4.3–4.9 (m, 1, CHOH), 7.4 (d, 1, quinoline 3 H, $J_{3,4}$ = 9 Hz), and 7.6–8.3 (m, 5, quinoline H).

*Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.85; H, 7.1; N, 6.55. Found: C, 78.9; H, 6.9; N, 6.4.

**2-(2-Quinolyl)cyclopentene (5).**—A mixture of the cyclopentanol **4** (0.25 g), powdered KOH (0.1 g), and hydroquinone (0.1 g) was heated slowly at 0.05 mm in a bulb tube until the cyclopentene **5** distilled (*ca.* 180°): yield 0.1 g (73%); ir $\nu_{max}^{film}$ 3030, 1615, and 1610 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 2.0–2.4 (m, 2), 2.5–3.4 (m, 4), 6.7–7.0 (m, 1, CH=), and 7.8–8.5 (m, 6, quinoline H). The hydrochloride had mp 160–162°.

*Anal.* Calcd for $C_{14}H_{13}N$: C, 86.1; H, 6.7; N, 7.15. Found: C, 86.0; H, 7.0; N, 7.0.

**Attempted Michael Condensations on 2-(2-Quinolyl)cyclopentene (5).**—The cyclopentene **5** failed to condense with the following reagents: (a) diethyl malonate with sodium ethoxide in ethanol, with sodium in toluene, or with potassium *t*-butoxide in *t*-butyl alcohol; (b) methyl, ethyl, or *t*-butyl cyanoacetate, all with *t*-butoxide in *t*-butyl alcohol.

**Methyl 1,2-Dihydro-2-quinolinylidenecyanoacetate (6).**—Methyl cyanoacetate (1.8 g) was added to a stirred solution of quinoline N-oxide (QNO) (2.5 g) in acetic anhydride (5.2 g) over 10 min. After 12 hr at 35–40°, the mixture was cooled, filtered, and the solid ester **6** crystallized from EtOH as yellow needles: mp 193–193.5°; yield 3.01 g (78%); nmr ($CDCl_3$) $\delta$ 3.88 (s, 3, $CH_3O$), 7.3–7.8 (m, 5), 7.98 (d, 1, $J$ = 9 Hz), and 13.6 (broad s, 1, NH).

*Anal.* Calcd for $C_{13}H_{10}N_2O_2$: C, 69.0; H, 4.45; N, 12.4. Found: C, 69.0; H, 4.3; N, 12.2.

***t*-Butyl 1,2-dihydro-2-quinolylidenecyanoacetate (7)** was prepared as above, using *t*-butyl cyanoacetate, in 65% yield: yellow needles, mp 209.5–210° dec; ir ($CCl_4$) 2205, 1640, and 1615 $cm^{-1}$; uv $\lambda_{max}$ (95% EtOH) 216, 286, and 394 m$\mu$; nmr ($CDCl_3$) $\delta$ 1.62 [s, 9, $C(CH_3)_3$], 7.2–8.1 (m, 6, quinoline H), 13.75 (broad s, 1, NH); nmr (TFA) $\delta$ 3.95 [s, 1, $CH(CN)CO_2$-*t*-Bu].

*Anal.* Calcd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.45. Found: C, 71.6; H, 5.95; N, 10.6

**1,2-Dihydro-2-quinolinylidenecyanoacetamide (8)** was prepared as was compound **6**, but reaction was vigorous and complete in 1 hr: mp 256–257°; yield 90%; ir (Nujol) 3390, 3330, 3265, 2190, 1633, and 1615 $cm^{-1}$.

*Anal.* Calcd for $C_{12}H_9N_3O$: C, 68.25; H, 4.3; N, 19.9. Found: C, 67.9; H, 4.15; N, 20.0.

**Ethyl 1,2-dihydro-2-quinolinylideneacetoacetate (9)** was prepared as described for compound **6**; after reaction was complete, excess acetic anhydride was decomposed by MeOH, and the residue after evaporation was dissolved in ether and shaken with aqueous $NaHCO_3$. Distillation of the dried ethereal extracts gave the ester **9** as a yellow oil: bp 155–164° (0.1 mm); yield 86%; crystallized on standing; recrystallization from petroleum ether (bp 60–80°) gave mp 58.5–59°; ir ($CCl_4$) 1690, 1632, and 1615 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.4 (t, 3, $J$ = 7 Hz, $CH_2CH_3$), 2.4 (s, 3, $COCH_3$), 4.3 (q, 2, $J$ = 7 Hz, $OCH_2CH_3$), 7.1–7.7 (m, 4 benzene ring), 7.81 (d, 1, $J$ = 8 Hz, quinoline 3), and 8.1 (d, 1, $J$ = 8 Hz, quinoline 4).

*Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.9; N, 5.45. Found: C, 70.2; H, 5.9; N, 5.6.

**Ethyl 2-(2-Quinolyl)propionate (10).**—A solution of ester **9** (0.56 g) in DME (20 ml) was added to a stirred mixture of NaH (0.06 g) in DME (40 ml). The mixture was boiled for 30 min and cooled, and methyl iodide (0.32 g) in DME (10 ml) was added over 15 min. The mixture was boiled for 30 min and evaporated, and the residue was treated with water, acidified with aqueous HCl (3 *N*, 50 ml), and extracted with ether. The acid extracts were basified, the free base was extracted with ether and the ether was evaporated to give the ester **10** (0.45 g, 90%), identical with a specimen prepared as previously described.[1]

**Ethyl 2-Quinolylacetate (11). A.**—Ethyl chloroformate (86 g, 0.8 mol) was added to a stirred solution of quinaldyllithium (0.5 mol) at −78° over 1 hr; the yellow mixture was allowed to come to room temperature over 2 hr. The ice-cooled mixture was decomposed with HCl (3 *N*, 200 ml) and separated, and the ether layer was further washed with HCl. The combined acid extracts were neutralized ($Na_2CO_3$) and extracted with ether. The residue from the dried ethereal extracts was distilled, giving quinaldine (23.4 g), ethyl 2-quinolylacetate (18.6 g, 17%), bp 130–135° (0.2 mm), and diethyl 2-quinolylmalonate (**12**) (25.6 g, 18%), bp 170–175° (0.2 mm). The malonate **12** solidified on standing and was crystallized from petroleum ether as yellow needles: mp 72–73° (lit.[7] mp 73–74°); ir $\nu_{max}^{Nujol}$ 1630 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.28, 1.31 (overlapping t, 6, $OCH_2CH_3$), 4.24 (q, 4, $OCH_2CH_3$), 7–8.2 (m, 6, aromatic H); some specimens showed a sharp peak at 5.05, less than 1 H, due to tautomer; nmr (TFA) $\delta$ 1.45 (t, 6, $OCH_2CH_3$), 4.55 (q, 4, $OCH_2CH_3$), 5.75 [s, 1, $CH(CO_2Et)_2$], 8.0–8.6 (m, 5), and 9.28 (d, 1, $J$ = 8 Hz, quinoline 4 H).

The malonate **12** was converted directly into ethyl 2-quinolylmalonate by a procedure described by Breslow[25] for another substituted malonate. Decarboxylation of the half-ester occurred at 120°: yield 88%.

**B.**—The keto ester **9** was treated as described above for the preparation of ester **10**, but no methyl iodide was added. Working up as before gave a quantitative yield of ethyl 2-quinolylacetate.

**C.**—2-Chloromethylquinoline[26] was converted into 2-cyanomethylquinoline.[27] 2-Cyanomethylquinoline (44.1 g) in absolute etOH (400 ml) containing added $H_2O$ (6 ml) was saturated with dry HCl at 60°, and the solution was boiled for 3 hr. Working up as described in ref 1 gave ethyl 2-quinolylacetate, bp 136–140° (0.04 mm), yield 43 g (75%).

**Ethyl 2-Acetyl-2-(2-quinolyl)propionate (13).**—A solution of keto ester **9** (2.2 g) in dry DME (10 ml) was added to a stirred suspension of NaH (0.42 g, 50% dispersion) in DME (20 ml) and allowed to stand for 2 hr. Methyl iodide (1.2 g) was added, and the mixture was stirred for 3 hr. Glacial acetic acid (1 ml) was added and the solvent was evaporated *in vacuo*, giving an orange oil (2.14 g), predominantly ester **13**: nmr ($CCl_4$) $\delta$ 1.30 (t, 3, $OCH_2CH_3$), 1.81 (s, 3, $CCH_3$), 2.20 (s, 3, $COCH_3$), 4.31 (q, 2, $OCH_2CH_3$), and 7.4–8.4 (m, 6, aromatic). Attempts at column chromatography or distillation led to decomposition, giving ester **10**.

**General Bromination Procedure for 2-Quinolylidenemalonates and Cyanoacetates 6–12.**—An equivalent amount of bromine in chloroform was added to the quinolylidene derivative, also in chloroform. After a short period at room temperature, the chloroform solution was shaken with saturated $NaHCO_3$, dried, and evaporated. Properties of compounds **14–17** are reported in Table I.

**Diethyl 1,2,3,4-Tetrahydroquinolylidenemalonate (18).**—The malonate **12** (2.2 g) in glacial AcOH (930 ml) was hydrogenated over Adams' catalyst at ambient temperature and pressure until uptake ceased. Evaporation, treatment of the residue with aqueous $NaHCO_3$ and ether, filtration, and evaporation of the dried ether solution gave a yellow solid, crystallized from petroleum ether as yellow plates (2 g, 90%): mp 40–41°; ir $\nu_{max}^{Nujol}$ 1688, 1648, 1250, and 747 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.32 (*t*, 6, $OCH_2CH_3$), 2.82 (*s*, 4), 4.22 (q, 4, $OCH_2CH_3$), and 6.7–7.3 (m, 4, aromatic); nmr (TFA) $\delta$ 1.1 (*t*, 6), 2.6–7.3 (m, 4), 3.9–4.6 [m, 5, includes $CH(CO_2Et)_2$], and 7.1 (broadened s).

*Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.85. Found: C, 66.7; H, 6.49; N, 4.9.

**Ethyl 2-(2-Quinolyl)cyclopentanone-2-carboxylate (19).**—2-Carbethoxycyclopentanone (82 g) was added to a stirred, cooled, (ice–water) solution of QNO (76 g) in acetic anhydride (70 g); the mixture was then allowed to stand overnight at room temperature. Methanol (25 ml) was added, the mixture was evaporated on a water bath (water pump), and the residual oil was dissolved in ether. After several extractions with $NaHCO_3$, the ethereal solution was dried and distilled. The keto ester **19** (130.6 g, 87%) had bp 150–155° (0.2 mm); ir $\nu_{max}^{film}$ 1726, 1725, and 758 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.26 (t, 3, $OCH_2CH_3$), 1.7–3.7 (m, aromatic).

*Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.05; H, 6.05; N, 4.95. Found: C, 72.1; H, 6.25; N, 4.9.

***t*-Butyl 2-(2-quinolyl)cyclopentanone-2-carboxylate (20)** was prepared as described for compound **19** in 69% yield. The keto ester **20** was an orange oil: bp 143–146° (0.0006 mm); ir $\nu_{max}^{film}$

(25) D. S. Breslow, E. Baumgarten, and E. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1287 (1944).

(26) W. Mathes and H. Schüly, *Angew. Chem.*, **75**, 235 (1963).

(27) V. Carelli, M. Cardellini, F. Liberatore, *Ann. Chim.* (Rome), **49**, 709 (1959).

TABLE I

PROPERTIES OF α-BROMOMETHYLQUINOLINES 14–17

| Compd | Yield, % | Mp, °C | Ir, cm⁻¹ | Nmr, δ, ppm | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N | Molecular formula |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 14 | 92 | 101–102[a] | 2207, 1743[b] | 4.02 (s, 3), 7.6–8.25 (m, 5) 8.45 (d, 1)[c] | 51.1 | 2.95 | 9.2 | 51.4 | 2.85 | 9.2 | $C_{13}H_9BrN_2O_2$ |
| 15 | 88 | 84–87[d] | 2210, 1775, 1750[b] | 1.65 (s, 9)[c] | 55.35 | 4.3 | 8.05 | 55.5 | 4.25 | 8.0 | $C_{16}H_{15}BrN_2O_2$ |
| 16 | 90 | 125–126[a] | 3470, 3400, 3260, 2190, 1717[e] | 7.6–8.3 (m, 7), 8.5 (d, 1)[c] | 49.65 | 2.75 | 14.5 | 50.0 | 2.75 | 14.7 | $C_{12}H_8BrN_3O$ |
| 17 | 97 | Oil | 1750[b] | 1.35 (t, 6), 4.44 (q, 4), 7.3–8.05 (m, 5), 8.24 (d, 1)[b] | 52.45 | 4.35 | 3.85 | 52.3 | 4.1 | 3.8 | $C_{16}H_{16}BrNO_4$ |

[a] Crystallized from petroleum ether. [b] $CCl_4$ solution. [c] $CDCl_3$ solution. [d] Crystallized from EtOH. [e] Nujol mull.

1758, 1728, and 760 cm⁻¹; nmr ($CCl_4$) δ 1.43 [s, 9, $OC(CH_3)_3$], 1.8–3.6 (m, 6, cyclopentanone H), 7.4–8.3 (m, 6, aromatic).

*Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.3; H, 6.8; N, 4.5. Found: C, 73.4; H, 6.5; N, 4.9.

**Oxidation of Keto Ester 19.**—A solution of keto ester **19** (3 g) in AcOH (50 ml) and $H_2O_2$ (30%, 30 ml) was heated on a water bath for 3 hr; a further 15 ml of $H_2O_2$ was added and heating was continued for 4 hr. The mixture was evaporated under reduced pressure and the residue was shaken with aqueous KOH and $CHCl_3$. The aqueous layer was separated and made just acid (3 *N* HCl); the free acid was extracted with chloroform and the chloroform was evaporated to give a solid. Recrystallization from methanol gave quinaldinic acid N-oxide, mp 166–168° dec, showing no depression in a mixture melting point with a sample obtained by oxidation of ethyl 2-quinolylacetate.

**5-(2-Quinolyl)pentanoic Acid (21). A.**—The keto ester **19** (3 g) was shaken with dilute aqueous ethanolic KOH solution until a homogeneous solution was obtained (15 min). The solution was just neutralized (3 *N* HCl) and evaporated; the residue was shaken with ether and water and the ether layer on evaporation gave the acid **21**, recrystallized from petroleum ether as colorless prisms: mp 93–94°, yield 2.2 g (90%); ir $\nu_{max}^{Nujol}$ 2800–2500, 1691, and 752 cm⁻¹; nmr given in text.

*Anal.* Calcd for $C_{14}H_{15}NO_2$: C, 73.35; H, 6.6; N, 6.1. Found: C, 73.3; H, 6.35; N, 6.1.

**B.**—The keto ester **20** (3.2 g) was hydrolyzed by 2 *N* HCl (30 ml) on a water bath (25 min). The yield of acid **21** was 2.3 g (100%).

**2-(2-Quinolyl)-2-cyanocyclopentanone (22).**—A dropwise addition of 2-cyanocyclopentanone (5.45 g) to a solution of QNO (7.25 g) in acetic anhydride (10 ml) caused an exothermic reaction; ice cooling was required. After 1 hr at room temperature, the mixture was cooled to −5° and the mixture of solid and oil which could be removed by filtration was extracted by petroleum ether to give the ketonitrile **22** (8.0 g, 68%). Recrystallization from petroleum ether gave yellow plates: mp 91–92°; ir $\nu_{max}^{Nujol}$ 2242 and 1768 cm⁻¹; nmr ($CDCl_3$) δ 2.0–3.4 (m, 6, cyclopentane), 7.4–8.2 (m, 5, aromatic), and 8.4 (d, 1, quinoline 4 H).

*Anal.* Calcd for $C_{15}H_{12}N_2O$: C, 76.35; H, 5.1; N, 11.85. Found: C, 75.8; H, 4.95; N, 11.7.

**5-Cyano-5-(2-quinolyl)pentanoic Acid (23).**—The cyano ketone **22** (0.5 g) was warmed gently with dilute aqueous $NaHCO_3$ until solution occurred. The mixture was neutralized (HCl) and extracted with chloroform, and the chloroform was dried and distilled. The residue was the cyano acid **23** (0.52 g, 94%), mp 118–120°; recrystallization from petroleum ether–ethanol only raised this to mp 119–120°; ir $\nu_{max}^{Nujol}$ 2240 and 1722 cm⁻¹; nmr ($CDCl_3$) δ 2.1 (m, 4), 2.48 (t, 2, $CH_2CO_2H$), 4.38 (t, 1, CHCN), 7.6–8.5 (m, 6, quinoline H), and 10.98 (broad s, 1, $CO_2H$).

*Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.4; H, 5.4; N, 10.8.

**2-(2-Quinolylacetyl)cyclopentane-1,3-dione (25)** was prepared as described for compound **22** and recrystallized from petroleum ether. It formed orange needles: mp 240–242°; yield 73%; ir $\nu_{max}^{Nujol}$ 1680 and 1640–1605 (broad) cm⁻¹; nmr (TFA) given in text.

*Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N, 5.25. Found: C, 71.45; H, 4.8; N, 5.4.

**2-(2-Quinolylacetimino)cyclopentane-1,3-dione (26).**—A solution of triketone **25** (1.6 g), malononitrile (0.35 g), and ammonium acetate (0.2 g) in benzene–ethanol was boiled for 12 hr. Evaporation and recrystallization of the residue from petroleum ether gave the imine **26** as colorless needles: mp 185–186°; yield 1.1 g (66%); ir $\nu_{max}^{Nujol}$ 3250, 1685, and 1625 cm⁻¹; nmr ($CDCl_3$) δ 2.57 (s, 4, cyclopentane), 4.87 (s, 2, $CH_2C{=}NH$), and 7.4–8.4 (m, 7, aromatic + NH).

*Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.15; H, 5.3; N, 10.5. Found: C, 71.75; N, 5.35; N, 10.5.

**Attempted Condensations with Keto Ester (19). A.**—The keto ester **19** was heated with ethyl cyanoacetate and ammonium acetate in benzene for 40 hr; only starting material was isolated. Similar lack of reaction was shown using piperidine as catalyst, or a mixture of piperidine and benzylamine at 110°.

**B.**—Boiling a solution of the keto ester **19** with ethyl cyanoacetate in acetic anhydride gave no identifiable condensation product.

**Ethyl 2-(2-Quinolyl)cyclopentanol-2-carboxylate (27).**—A solution of keto ester **19** (10 g) in ethanol (100 ml) was hydrogenated at atmospheric temperature and pressure until absorption ceased. The residue after filtration and evaporation was distilled to give the cyclopentanol **27**: bp 155–160° (0.1 mm); yield 8.8 g, (87%); ir $\nu_{max}^{film}$ 1725 and 752 cm⁻¹.

*Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.65; N, 4.9. Found: C, 71.7; H, 6.62; N, 5.2.

**2-(1,3-Dioxolanyl)-1-(2-quinolyl)cyclopentanecarboxylic Acid Esters (28 and 29).**—A solution of the appropriate ester (**19** or **20**) with an equivalent amount of ethylene glycol was ketalized in boiling toluene using *p*-toluenesulfonic acid; after removal of the toluene, Girard-T was used to remove unreacted keto ester. The nonketonic residue was an orange oil. Chromatography on Woelm alumina (grade IV) in benzene gave the ketal **28** as a pale yellow liquid: yield 42%; ir $\nu_{max}^{film}$ 1725 and 750 cm⁻¹; nmr ($CCl_4$) δ 1.08 (t, 3, $OCH_2CH_3$), 1.4–2.6 (m, 6, cyclopentane H), 3.6–6.4 (m, 6, $OCH_2CH_3$ and $OCH_2CH_2O$), 7.3–8.0 (m, 5, quinoline H), and 8.16 (d, 1, quinoline 4 H).

*Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.45; N, 4.3. Found: C, 69.1; H, 6.6; N, 4.3.

Ketal **29** (yield 36%) had ir $\nu_{max}^{film}$ 1725 and 752 cm⁻¹; nmr ($CCl_4$) δ 1.43 [s, 9, $OC(CH_3)_3$]; otherwise as described for **28**.

*Anal.* Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.1; N, 3.95. Found: C, 70.5; H, 7.15; N, 4.2.

**2-(1,3-Dioxolanyl)-1-(1,2,3,4-tetrahydro-2-quinolyl)cyclopentanecarboxylic Acid Esters (30 and 31).**—A solution of the ketal **28** (4.5 g) in glacial AcOH was hydrogenated at atmospheric pressure and room temperature over Adams' catalyst (200 mg) until 2 mol equiv were absorbed. Evaporation was followed by treatment with aqueous $NaHCO_3$ and ether and filtration, and the ethereal layer was removed, dried, and evaporated. The residual oil was chromatographed (Woelm alumina, grade III) in benzene, giving unchanged ketal **28** (0.7 g) and the tetrahydro ketal **30** (3.6 g, 94% on unrecovered starting material): ir $\nu_{max}^{film}$ 3410, 1725, and 750 cm⁻¹; nmr ($CCl_4$) δ 1.26 (t, 3, $OCH_2CH_3$), 1.4–6.3 (m, 18), and 6.3–7.0 (m, 4, aromatic H).

*Anal.* Calcd for $C_{19}H_{25}NO_4$: C, 68.85; H, 7.55; N, 4.2. Found: C, 68.3; H, 7.4; N, 4.1.

**31** was similarly prepared (88%): ir $\nu_{max}^{film}$ 3405, 1725, and 753 cm⁻¹; nmr ($CCl_4$) δ 1.44 [s, 9, $C(CH_3)_3$] overlaying 1.4–2.0 (m, 2), 2.2–2.9 (m, 6), 3–3.9 (m, 5), 4.0–4.3 (m, 3), and 6.2–7.1 (m, 4, ArH).

*Anal.* Calcd for $C_{21}H_{29}NO_4$: C, 70.15; H, 8.15; N, 3.9. Found: C, 69.6; H, 8.05; N, 3.8.

TABLE II

PROPERTIES OF ENOL ACETATES 49–53

| Compd | $R_1$ | $R_2$ | Bp, °C (mm) | Yield, % | Ir, $cm^{-1}$ | Nmr, $\delta$ ppm | Molecular formula | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **49** | $CH_3$ | CN | 70–72 (0.1) | 35 | 2228, 1780 1660[a] | 2.22 (s, 3)[b] | $C_8H_9NO_2$ | 63.55 | 6.0 | 9.25 | 63.8 | 5.8 | 9.6 |
| **50** | $CH_2Cl$ | $CO_2Et$ | 90–92 (0.05) | 61 | 1790, 1728 1663[a] | 1.28 (t, 3) 4.2 (q, 2) 4.35 (s, 2)[b] | $C_{10}H_{13}ClO_4$ | 51.5 | 5.6 | ··· | 51.1 | 5.45 | ··· |
| **51** | $CH_2Cl$ | CN | 112–115 (0.1) | 50 | 2230, 1790 1662[a] | 4.35 (s, 2)[b] | $C_8H_8ClNO_2$ | 51.75 | 4.3 | 7.55 | 51.5 | 4.35 | 7.3 |
| **52** | $CH_2OEt$ | $CO_2Et$ | 102–105 (0.1) | 76 | 1788, 1730 1658, 1108[a] | 1.1–1.6 (m, 6) 3.66 (q, 2) 4.2 (q, 2) 4.26 (s, 2)[b] | $C_{12}H_{18}O_5$ | 59.55 | 7.45 | ··· | 59.0 | 7.5 | ··· |
| **53** | $CH_2OEt$ | CN | 98–100 (0.1) | 92 | 2225, 1788 1655, 1108[a] | 1.25 (t, 3) 3.65 (q, 2) 4.25 (s, 2)[b] | $C_{10}H_{13}NO_3$ | 61.5 | 6.7 | 7.2 | 61.8 | 6.55 | 7.1 |

[a] Liquid film. [b] $CCl_4$ solution.

**Attempted Alkylation of the Ketal 30. A.**—A solution of the ketal **30** (3 g) and acrylonitrile (4 g) in acetic acid (50 ml) with a little cuprous chloride (0.1 g) was boiled for 20 hr. Filtration and evaporation of the solution gave unreacted ketal.

**B.**—Similar treatment at 150° for 4 hr in a sealed tube gave a crude product from which no identifiable material could be obtained.

**Ethyl 2-Carbethoxy-2-(2-quinolyl)cyclopentylidenecyanoacetate (40).**—The cyano ester **32** (20 g) was condensed with QNO (11.8 g) in the usual way; chromatography of the product on alumina (Woelm, grade IV) in a benzene–petroleum ether mixture gave a small amount of recovered cyano ester **32** (1.2 g) and the cyclopentylidene cyanoac etate **40** (19.6 g, 65%) as an orange oil, very unstable in air: ir $\nu_{max}^{film}$ 2230, 1730, and 1625 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.0–1.5 (m, 6, $OCH_2CH_3$), 1.6–3.3 (m, 6, cyclopentane), 3.8–4.5 (m, 4, $OCH_2CH_3$), and 7.3–8.3 (m, 6, quinoline H).

*Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.8; H, 5.85; N, 7.4. Found: C, 69.5; H, 5.7; N, 7.1.

**Attempted Ethanolysis of Cyano Ester 40.**—The cyano ester **40** was treated with a boiling ethanolic HCl solution for 3 hr, and with boiling ethanolic sulfuric acid for 3 hr; in both cases, the products still showed C=N stretching in the ir. Longer periods of reaction showed no further reaction.

**Attempted Alcoholysis of Cyano Ester 32. A.**—A solution of cyano ester **32** (5 g) in ethanol (50 ml) containing concentrated $H_2SO_4$ (2 ml) was boiled for 5 hr. To the cooled mixture was added chloroform (150 ml) and aqueous $NaHCO_3$, the mixture was filtered, and the chloroform was separated, dried, and evaporated, giving the pyridine **42**: mp 220° dec (lit.[17] mp 238–240°); yield 1.9 g; ir $\nu_{max}^{Nujol}$ 3370, 3120, 2800, 2700, 1655, and 1620 $cm^{-1}$; nmr (TFA) $\delta$ 1.56 (t, 3, $OCH_2CH_3$), 2.42 (q, 2), 3.06 (t, 2), 3.55 (t, 2), and 4.70 (q, 2, $OCH_2CH_3$).

*Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.2; H, 5.85; N, 6.3. Found: C, 59.6; H, 5.8; N, 6.3.

**B.**—The cyano ester **32** (6 g) in methanol (100 ml) was saturated with dry HCl and the solution was boiled for 3 hr. Evaporation gave a residue containing solid. Filtration and recrystallization of the solid from EtOH gave the pyridine **43** as needles: mp 227–229° dec; yield 1.8 g; ir $\nu_{max}^{Nujol}$ 3370, 3120, 2800, 2700, 1655, and 1620 $cm^{-1}$; nmr (TFA) $\delta$ 2.0–2.6 (m, 2), 2.7–3.2 (t, 2), 3.2–3.6 (m, 2), and 4.12 (s, 3).

*Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 57.2; H, 5.25; N, 6.6.

**Dimethyl 2-Carbomethoxycyclopentylidenemalonate (34) and Its Condensation with Quinoline N-Oxide.**—A solution of the cyano ester **32** (8.1 g) and KOH (12 g) in aqueous ethanol (1:1, 60 ml) was boiled for 8 hr and evaporated, and the residue was dissolved in water and acidified. The free acid was extracted by chloroform and recovered by evaporation (4.2 g). The crude acid was dissolved in methanol (50 ml) with sulfuric acid (2 ml) and the mixture was boiled. The cooled mixture was diluted with benzene (50 ml), washed with aqueous $NaHCO_3$, dried, and distilled. The triester **34** (3.8 g) had bp 80–82° (0.2 mm). The nmr spectrum had a ratio of ester to cyclopentane protons of slightly less than 3:2. The crude triester **34** (3 g) was condensed with QNO (2.2 g) in acetic anhydride (3 ml) overnight at 40–50°; the solid which separated was recrystallized as yellow prisms of the biquinolyl malonate **44**: mp 209–210°; yield 1.6 g (55%); ir $\nu_{max}^{Nujol}$ 1750 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 4.05 (s) and 7.4–8.4 (m) in ratio 1:2.

*Anal.* Calcd for $C_{23}H_{18}N_2O_4$: C, 71.5; H, 4.7; N, 7.25. Found: C, 70.9; H, 4.65; N, 7.2.

**Di(2-quinolyl)methane.**—A solution of the diester **44** (1 g) in 20% aqueous HCl (20 ml) was boiled for 2 hr and evaporated, and the residue was basified and extracted with chloroform. The chloroform extracts were dried and evaporated, giving a solid, recrystallized from petroleum ether as light brown needles, mp 105–106° (lit.[19] mp 107°).

**Cyclopentylidenemalonitrile (35).**—A few drops of piperidine were added to a solution of malononitrile (13.2 g) and cyclopentanone (16.8 g) in chloroform; an exothermic reaction occurred. After 10 min, the chloroform solution was shaken with dilute acid and water, dried, and distilled. The nitrile **35** (22 g, 83%) had bp 80° (0.2 mm); ir $\nu_{max}^{film}$ 2240 and 1615 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.8–2.2 (m, 4) and 2.6–3.1 (m, 4).

*Anal.* Calcd for $C_8H_8N_2$: C, 72.7; H, 6.1; N, 21.2. Found: C, 72.3; H, 6.05; N, 21.6.

**6-Amino-5,5,7-tricyano-4-spirocyclopentyl-3,3a,4,5-tetrahydro-2H-indene (45)** was obtained when an ethanol solution of cyclopentanone and malononitrile was treated with piperidine and allowed to stand for 30 min. The solid which separated was filtered and recrystallized from ethanol to give the indene **45**: mp 184–186°; ir $\nu_{max}^{CHCl_3}$ 3465, 3385, 3200, 2220, and 1632 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.5–2.2 (m, 10), 2.3–2.8 (m, 2, $CH_2C$=) 2.95–3.4 (m, 1, CH–C=) 5.2–5.6 (br s, 2, $NH_2$), and 5.8–6.0 (m, 1, CH=C).

*Anal.* Calcd for $C_{18}H_{16}N_4$: C, 72.7; H, 6.1; N, 21.2. Found: C, 73.0; H, 6.05; N, 21.7.

***t*-Butyl Cyclopentylidenecyanoacetate (37).**—A mixture of *t*-butyl cyanoacetate (70 g), 2-carbomethoxycyclopentanone (70 g), and piperidine (a few drops) in xylene (200 ml) was boiled for 12 hr, the xylene was removed, and the residue was distilled. From the *t*-butyl cyanoacetate fraction, a solid crystallized; this was separated and recrystallized from ethanol to give the cyano ester **37**: mp 87–88°; yield 14.2 g (14%); ir $\nu_{max}^{Nujol}$ 2230 and 1720 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.6 [s, 9, $C(CH_3)_3$], 1.7–2.3 (m, 4), and 2.6–3.3 (m, 4, $CH_2$–C=).

*Anal.* Calcd for $C_{12}H_{17}NO_2$: C, 69.55; H, 8.25; N, 6.75. Found: C, 69.4; H, 8.25; N, 6.8.

**Cyclopentylidenecyanoacetic Acid.**—The cyano ester **37** (1 g) was heated at 220° (15 mm) until evolution of gas ceased. Recrystallization of the residue gave cyclopentylidenecyanoacetic acid: mp 132–132.5°; ir $\nu_{max}^{Nujol}$ 2600 (br), 2232, and 1700 $cm^{-1}$; nmr ($CDCl_3$) $\delta$ 1.7–2.2 (m, 4), 2.7–3.3 (m, 4), and 10.35 (s, 1, $CO_2H$).

*Anal.* Calcd for $C_8H_9NO_2$: C, 63.6; H, 5.95; N, 9.3. Found: C, 63.0; H, 5.9; N, 9.1.

**Isopropylidene Cyclopentylidenemalonate (38).**—A mixture of cyclopentanone (8.4 g), isopropylidene malonate (14.4 g), piperidine (a few drops), and pyridine (5 ml) was kept at 40–50° for 12 hr. The mixture was cooled (−5°) until precipitation was complete, then filtered. The malonate **38**, (12.8 g, 61%) formed colorless needles from petroleum ether: nmr ($CCl_4$) $\delta$ 1.7 [s, 6, $(CH_3)_2C$], 1.6–2.1 (m, 4, cyclopentane H), and 3.0–3.4 (m, 4, $CH_2C$=).

*Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.7. Found: C, 63.2; H, 6.5.

**1-Acetyl-4-(2-Keto-1-carbethoxycyclopentyl)-1,4-dihydroquinoline (47).**—Acetyl chloride (2.3 g) was added dropwise to a solution of quinoline (11.6 g) and 2-carbethoxycyclopentanone (4.7 g) in dry benzene (150 ml). A precipitate of quinoline hydrochloride slowly formed; after 3 days at room temperature, the smell of acetyl chloride had disappeared. The quinoline hydrochloride was filtered off, and the precipitate was washed with ether. The combined filtrates were shaken with 2 *N* HCl (three 50-ml portions) and aqueous $Na_2CO_3$, dried, and evaporated. Crystallization of the residue from petroleum ether gave colorless cubes of the acetylquinoline **47**: mp 138–140°; yield 3.9 g (40%); ir $\nu_{max}^{CCl_4}$ 1750, 1720, 1690, and 1655 $cm^{-1}$; nmr discussed in the text.

*Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.45; N, 4.3. Found: C, 70.0; H, 6.55; N, 4.2.

**1-Acetyl-2-(2-keto-1-cyanocyclopentyl)-1,2-dihydroquinoline (48)** was prepared as described for compound **47** using 2-cyanocyclopentanone; reaction was complete in 1 hr. The crude product in this case was a mixture of liquid and solid. The solid was removed and crystallized to give the acetyl-1,2-dihydroquinoline **48**: mp 116–117°; yield 29%; ir $\nu_{max}^{CCl_4}$ 2245, 1752, 1642, and 1656 $cm^{-1}$; nmr discussed in the text.

*Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.85; H, 5.75; N, 10.0. Found: C, 72.8; H, 5.55; N, 9.9.

After removal of the solid, the filtrate was distilled, giving some 2-cyanocyclopentanone and 1-acetoxy-2-cyanocyclopentene, **49**: bp 70–72° (0.1 mm); yield 35%; ir $\nu_{max}^{film}$ 2228, 1780, and 1660 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 2.22 (s, 3, $OCOCH_3$), 1.8–2.2 (m, 2), and 2.3–2.8 (m, 4).

*Anal.* Calcd for $C_8H_9NO_2$: C, 63.55; H, 6.0; N, 9.25. Found: C, 63.8; H, 5.8; N, 9.6.

The enol acetates listed in Table II were similarly prepared from the appropriate acyl chlorides; no other dihydroquinolines were isolated.

**Registry No.**—**2**, 21372-65-6; **2** (HCl), 21372-66-7; **4**, 21369-00-6; **5**, 21369-01-7; **5** (HCl), 21369-02-8; **6**, 21369-03-9; **7**, 2859-27-0; **8**, 2859-28-1; **9**, 21369-06-2; **11**, 5100-57-2; **12**, 21369-08-4; **13**, 21369-09-5; **14**, 21369-10-8; **15**, 21369-11-9; **16**, 21369-12-0; **17**, 21369-13-1; **18**, 21369-14-2; **19**, 21369-15-3; **20**, 21369-16-4; **21**, 21369-17-5; **22**, 21369-18-6; **23**, 21369-19-7; **25**, 21369-20-0; **26**, 21369-21-1; **27**, 21369-22-2; **28**, 21389-70-8; **29**, 21369-23-3; **30**, 21369-24-4; **31**, 21615-81-6; **35**, 5660-83-3; **37**, 21369-27-7; **38**, 3968-30-7; **40**, 21369-29-9; **42**, 21369-30-2; **43**, 21369-31-3; **44**, 21369-32-4; **45**, 21369-33-5; **47**, 21369-34-6; **48**, 21369-35-7; **49**, 21369-36-8; **50**, 21369-37-9; **51**, 21369-38-0; **52**, 21369-39-1; **53**, 21369-40-4; quinaldinic acid N-oxide, 3297-64-1; cyclopentylidenecyanoacetic acid, 21369-42-6.

**Acknowledgment.**—Our thanks are due to the Science Research Council for a Fellowship (J. D. B.) and a Studentship (C. M.) and to Smith Kline and French Laboratories for financial support during part of the work.

# Oxygenation of Aromatic Compounds with Diisopropyl Peroxydicarbonate–Cupric Chloride[1]

PETER KOVACIC,[2] C. GLENN REID, AND MICHAEL E. KURZ

*Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, and Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201*

*Received February 11, 1969*

The direct synthesis of aryl isopropyl carbonates from a wide variety of aromatic substrates has been accomplished with the diisopropyl peroxydicarbonate–aromatic–cupric chloride system in acetonitrile at 60°. The orientation and relative rate data lend further support to the hypothesis that substitution is effected by a radical entity possessing appreciable electrophilic character. A Hammett–Brown treatment yielded a $\rho$ value of −2.3. Several reaction parameters were investigated, including photolytic conditions and variation in the amount of aromatic substrate.

The direct introduction of oxygen into the aromatic nucleus has been effected by an electrophilic pathway resulting from heterolytic cleavage[3a,4] or by radical attack *via* homolytic fission.[5a] In the former category, Lewis acids are frequently employed as catalysts in conjunction with hydrogen peroxide,[6] peroxy acids,[7] diaroyl peroxides,[8] and peroxydicarbonates,[9] while hydroxylation with Fenton reagent[10] and benzoyloxylation with benzoyl peroxide[5a,11] are illustrations of the radical type. Also, the production of benzoate esters in the aromatic–benzoyl peroxide–iodine system has been described by Perret and Perrot.[12]

Recently, reports[13,14] from this laboratory showed that aromatic oxygenation could be realized in high yield with diisopropyl peroxydicarbonate and small amounts of cupric chloride. The stoichiometry of the

(1) Aromtic Oxygenation. IX.

(2) To whom correspondence should be addressed: Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wis. 53201.

(3) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compunds," Elsevier Publishing Co., New York, N. Y., 1965: (a) Chapter 4; (b) p 85; (c) p 75; (d) p 51.

(4) L. S. Boguslavskaya, *Russ. Chem. Rev.*, **34**, 503 (1965).

(5) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, New York, N. Y., 1960: (a) Chapter 7; (b) p 68; (c) p 115.

(6) D. H. Derbyshire and W. A. Waters, *Nature*, **165**, 401 (1950); J. D. McClure and P. H. Williams, *J. Org. Chem.*, **27**, 24 (1962).

(7) A. J. Waring and H. Hart, *J. Amer. Chem. Soc.*, **86**, 1454 (1964); H. Hart and C. A. Buehler, *J. Org. Chem.*, **29**, 2397 (1964).

(8) D. Z. Denney, T. M. Valega, and D. B. Denney, *J. Amer. Chem. Soc.*, **86**, 46 (1964).

(9) P. Kovacic and M. E. Kurz, *J. Org. Chem.*, **31**, 2011 (1966).

(10) J. R. L. Smith and R. O. C. Norman, *J. Chem. Soc.*, 2897 (1963).

(11) G. B. Gill and G. H. Williams, *ibid.*, 7127 (1965).

(12) A. Perret and R. Perrot, *Helv. Chim. Acta*, **28**, 558 (1945).

(13) M. E. Kurz and P. Kovacic, *J. Org. Chem.*, **33**, 266 (1968).

(14) M. E. Kurz and P. Kovacic, *J. Amer. Chem. Soc.*, **89**, 4960 (1967).