Some 2(1H)-Quinolylidene Compounds. Synthesis, Structure, and Reactions[1]

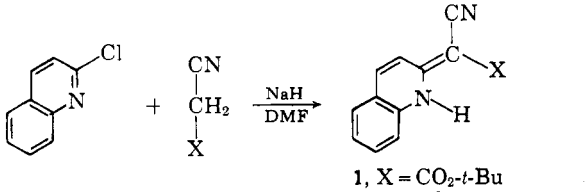
A. L. BORROR[2] AND A. F. HAEBERER[2]

Department of Chemistry, Harvard University, Cambridge, Massachusetts, and Department of Chemistry, Drexel Institute of Technology, Philadelphia, Pennsylvania

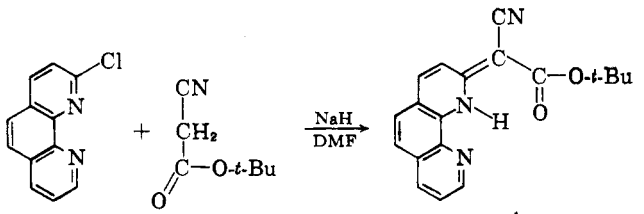
Received August 10, 1964

The reaction of 2-chloroquinoline with the sodium salts of *t*-butyl cyanoacetate, ethyl cyanoacetate, and malononitrile gives *t*-butyl cyano-2(1H)-quinolylideneacetate (**1**), ethyl cyano-2(1H)-quinolylidene acetate (**2**), and 2(1H)-quinolylidenemalonitrile (**3**), respectively. The structures assigned to these compounds are based upon infrared, ultraviolet, and n.m.r. spectroscopy. The reaction of 2-chloro-1,10-phenanthroline with *t*-butyl cyanoacetate yields *t*-butyl cyano-2-(1H)-1,10-phenanthrolylideneacetate (**4**). 2-Chloroquinoline reacts in an "abnormal" manner with cyanoacetamide to give 2-quinolyl-2(1H)-quinolylideneacetonitrile (**8**). The reactions of the esters **1**, **2**, and **4** with acid were studied.

We have found that 2-chloroquinoline reacts smoothly with the sodium salts of *t*-butyl cyanoacetate, ethyl cyanoacetate, and malononitrile to give *t*-butyl cyano-2(1H)-quinolylideneacetate (**1**), ethyl cyano-2(1H)-quinolylideneacetate (**2**), and 2(1H)-quinolylidenemalononitrile (**3**), respectively. Similarly, the reaction between 2-chloro-1,10-phenanthroline and the sodium salt of *t*-butyl cyanoacetate gives *t*-butyl cyano-2(1H)-1,10-phenanthrolylideneacetate (**4**).

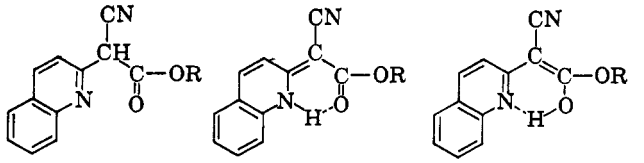


1, X = CO_2-*t*-Bu
2, X = CO_2Et
3, X = CN



4

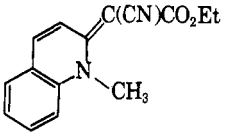
The aromatic nucleophilic substitution reaction of acyclic active methylene compounds with heterocyclic systems possessing a replaceable halogen has received some attention,[3] but tautomeric possibilities for the resulting products apparently were not considered. By analogy to pyrophthalone,[4,5] and 2-phenacylpyridine,[6] tautomeric forms such as **1a–c** and **2a–c**



1a, R = *t*-Bu **1b** **1c**
2a, R = Et **2b** **2c**

must be considered in assigning structures to 2-substituted quinolines when the attached substituent bears electron-withdrawing groups.

Ultraviolet and visible spectroscopy (Table I) indicate that the substitution products **1**, **2**, and **3** exist in the 2(1H)-quinolylidene form in chloroform solution. All three compounds show absorption maxima in the 400–440-mμ region indicating extended conjugation in comparison with simple quinoline systems. Furthermore, the spectra of these compounds are similar to that of ethyl cyano-2(1-methyl)-quinolylideneacetate (**5**),[7] the N-methyl analog of **2**. The ultraviolet and visible spectra of the *t*-butyl ester **1** and ethyl ester **2** are not changed appreciably in ethanol suggesting that the 2(1H)-quinolylidene form predominates in hydroxylic solvents also.



5

The infrared spectra of compounds **1**, **2**, and **3** when taken in potassium bromide pellets or chloroform solution remain essentially the same in the solid state as in solution; hence, they exist in the same tautomeric form in both phases. The infrared spectra are consistent with the 2(1H)-quinolylidene structure assigned on the basis of ultraviolet and visible spectroscopy. The spectra of the esters **1** and **2** show a conjugated nitrile at 2200 cm.$^{-1}$, the same position as found for ethyl cyano-2(1-methyl)quinolylideneacetate (**5**). The spectrum of the malononitrile derivative **3** shows split nitrile absorption at 2230 and 2200 cm.$^{-1}$. The ester carbonyl absorption for the *t*-butyl ester **1** and the ethyl ester **2** does not occur in the 1770–1700-cm.$^{-1}$ region which covers normal conjugated and nonconjugated esters. There is strong absorption at 1655 cm.$^{-1}$, but other types of unsaturation absorb in this region, complicating the peak assignment. The anomalous nature of the carbonyl absorption in the esters **1** and **2** also is reflected in the spectrum of the N-methyl ester **5**. No carbonyl absorption is found in the 1770–1700-cm.$^{-1}$ region, but there is strong absorption at 1675 cm.$^{-1}$. Assuming that the bands at 1655 and 1675 cm.$^{-1}$ are due to carbonyl absorption, these abnormal frequency shifts can be rationalized in terms of the contribution of structures such as **2b′** to the

(1) This problem was initiated at Harvard University by A. L. Borror with partial support by a grant from the National Science Foundation (NSF-G-14473) and continued at Drexel Institute of Technology.

(2) Department of Chemistry, Drexel Institute of Technology, Philadelphia, Pa.

(3) Y. Mizuno, K. Adachi, and K. Ikeda, *Pharm. Bull.* (Tokyo), **2**, 225 (1954); *Chem. Abstr.*, **50**, 1034*g* (1956).

(4) A. R. Katritzky and J. M. Lagowski, "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, p. 429.

(5) D. G. Manly, A. Richardson, A. M. Stock, C. H. Tilford, and E. D. Amstutz, *J. Org. Chem.*, **23**, 273 (1958).

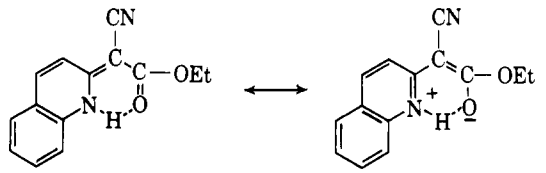
(6) R. F. Branch, *Nature*, **177**, 671 (1956).

(7) H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).

TABLE I

ULTRAVIOLET AND VISIBLE SPECTRA

Comp.	λ_{max}, mμ (CHCl₃)	log ε (CHCl₃)	λ_{max}, mμ (EtOH)	Log ε (EtOH)
t-Butyl cyano-2(1H)-quinolylideneacetate (1)	289, 390 (sh)	4.38, 4.16	285, 382 (sh)	4.42, 4.15
	405, 427	4.26, 4.14	396, 410 (sh)	4.24, 4.09
Ethyl cyano-2(1H)-quinolylideneacetate (2)	290, 386 (sh)	4.40, 4.15	287, 382 (sh)	4.43, 4.16
	403, 426	4.25, 4.09	398, 414 (sh)	4.25, 4.11
2(1H)-Quinolylidenemalononitrile (3)	290, 391 (sh)	4.40, 4.16	...	...
	411, 434	4.22, 4.00	...	...
Cyano-2(1H)-quinolylideneacetamide (6)	288, 386 (sh)	4.38, 4.14	...	...
	402, 426	4.25, 4.10	...	...
Ethyl cyano-2-(1-methyl)quinolylideneacetate (5)	294, 413	4.16, 4.29	...	...
	430 (sh)	4.20	...	...
t-Butyl cyano-2(1H)-1, 10-phenanthrolylideneacetate (4)	251, 310, 323	4.45, 4.18, 4.46	...	...
	368, 405 (sh)	4.01, 3.91	...	...
	426, 450 (sh)	3.98, 3.80	...	...
2-Quinolyl-2(1H)-quinolylideneacetonitrile (8)	276, 322 (sh)	4.37, 4.17	...	...
	363, 382, 432	3.84, 3.90, 4.23	...	...
	456, 485	4.43, 4.33	...	...



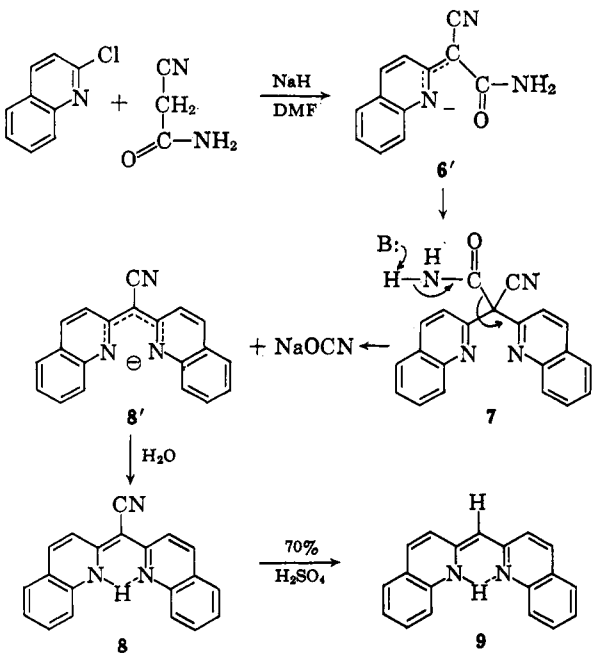
2b **2b′**

ground state of the molecules.[8] The frequency shift is more pronounced in *t*-butyl cyano-2(1H)-quinolylideneacetate (1) and ethyl cyano-2(1H)-quinolylideneacetate (2) than in the N-methyl ester 5, probably because of intramolecular hydrogen bonding effects.

The n.m.r. spectrum of *t*-butyl cyano-2(1H)-quinolylideneacetate (1) in deuteriochloroform shows a signal (nine protons) attributable to the methyl groups at 1.60 p.p.m., a complex set of signals from 7.1 to 7.8 p.p.m. due to six protons attached to the unsaturated carbons of the rings, and a single broad peak at 13.3 p.p.m. due to a single proton. This last peak occurs in the region of strongly hydrogen-bonded protons and is broadened by nitrogen as expected for structure 1. This n.m.r. spectrum is not consistent with structure 1a, which should not show a peak at 13.3 p.p.m. and which would show an aromatic proton pattern of the simple quinoline type.[9] It should be noted that the n.m.r. spectrum of 5 also confirms the structure of this compound (N–CH_3 singlet at 3.9 p.p.m., six-proton multiplet at 7.2–8.2 p.p.m. very similar to that of 1, and the expected C_2H_5O quartet and triplet).

Ultraviolet, visible, infrared, and n.m.r. spectra, when taken together, support the 2(1H)-quinolylidene structure for compounds 1, 2, and 3. Although less thoroughly studied, the structural assignment for *t*-butyl cyano-2(1H)-1,10-phenanthrolylideneacetate (4) is consistent with the electronic absorption spectrum and infrared spectrum of this compound. The compound is colored and shows an absorption maximum in the visible region (Table I) at slightly longer wave lengths than the 2(1H)-quinolylidene compounds. The infrared spectrum reveals a conjugated nitrile at 2200 cm.$^{-1}$; there is no ester carbonyl absorption in the normal 1770–1700-cm.$^{-1}$ region, but there is strong absorption at 1650 cm.$^{-1}$ analogous to the esters 1 and 2.

The reaction of 2-chloroquinoline with the sodium salt of cyanoacetamide did not give the expected product, cyano-2(1H)-quinolylideneacetamide (6), under conditions described for the synthesis of compounds 1, 2, and 3. Instead an orange, high-melting solid was obtained. This compound was assigned the structure, 2-quinolyl-2(1H)-quinolylideneacetonitrile (8). Analysis and spectroscopic evidence agreed with this assignment. The infrared spectrum of the compound shows conjugated nitrile absorption at 2200 cm.$^{-1}$; the electronic absorption spectrum points to a highly conjugated system (Table I). The melting point (284°) is four degrees higher than that previously reported in the literature[10] for this compound but, in agreement with the literature, compound 8 is hydrolyzed by 70% sulfuric acid to 2-quinolyl-2(1H)-quinolylidenemethane (9).[11]



(8) *Cf.* L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 255.

(9) P. J. Black and M. L. Hefferman, *Australian J. Chem.*, **17**, 559 (1964).

(10) H. J. Friedrich, W. Guckel, and G. Scheibe, *Chem. Ber.*, **95**, 3781 (1962).

(11) G. Sheibe and H. J. Friedrich, *ibid.*, **94**, 1336 (1961).

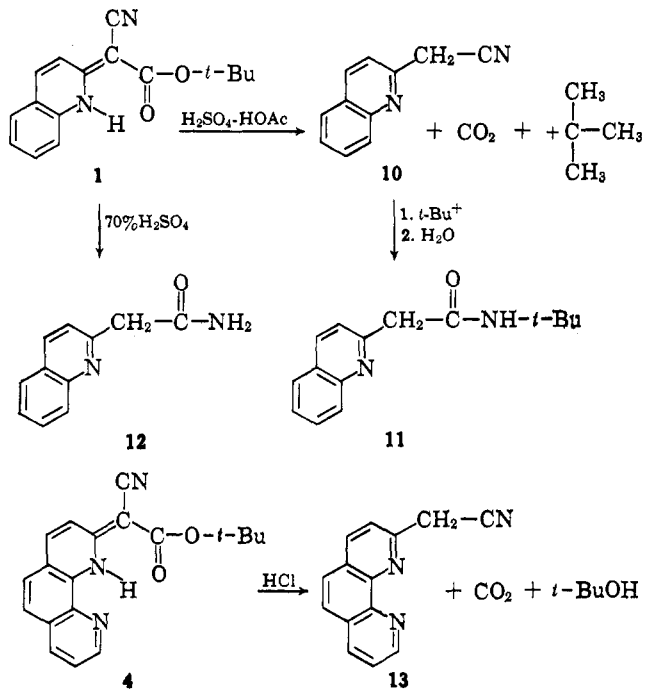
The yield of 2-quinolyl-2(1H)-quinolylideneacetonitrile (**8**) from the reaction was 34% and was not improved by prolonged reaction times and somewhat higher temperatures. The reaction mixture was not complex; compound **8** was separated readily from unchanged starting materials.

A plausible mechanism for this reaction involves the formation of cyano-2(1H)-quinolylideneacetamide (**6**) which in the presence of strong base is converted to the anion **6'**. Subsequent reaction of the anion **6'** with unchanged 2-chloroquinoline gives 2,2'-diquinolylcyanoacetamide (**7**). A novel elimination of isocyanic acid, initiated by abstraction of a proton from the NH_2 group, would yield the extremely stable anion **8'**. Aqueous work-up furnishes the observed product, **8**. Consistent with the proposed mechanism, sodium cyanate can be isolated from the reaction mixture. By carrying out the reaction at 50° for 1 hr., a small yield of the proposed intermediate, cyano-2(1H)-quinolylideneacetamide (**6**), also can be isolated.

The 2(1H)-quinolylidene compounds discussed above did not form salts in dilute acid solution. Protonation, it is to be noted, would destroy the extended conjugation present in the system. The inertness of ethyl cyano-2(1H)-quinolylideneacetate (**2**) toward alkaline hydrolysis is probably related to conjugative stabilization; the ester was recovered unchanged after boiling with alcoholic potassium hydroxide. Prolonged boiling with aqueous hydrochloric acid did result in hydrolysis and concomitant decarboxylation to give an oil with an infrared spectrum identical with that of quinaldine.

It was found that *t*-butyl cyano-2(1H)-quinolylideneacetate (**1**) also is inert toward alkaline hydrolysis. Attempted acid-catalyzed decomposition of the ester by *p*-toluenesulfonic acid in boiling benzene was unsuccessful. Reaction did occur with fuming sulfuric acid in acetic acid to give a colorless compound, $C_{15}H_{18}N_2O$ (**11**), in 62% yield. We have assigned to compound **11** the structure 2-quinolyl-N-*t*-butylacetamide. The infrared spectrum of compound **11** points to an amide with an N–H stretching band at 3300 cm.$^{-1}$ and carbonyl absorption at 1640 cm.$^{-1}$; no nitrile absorption is present. The n.m.r. spectrum strongly supports the assignment for **11**. In addition to a sharp peak due to nine protons at 1.35 p.p.m. (*t*-butyl) there is a sharp peak due to two protons at 3.8 p.p.m. (methylene) and a multiplet between 7.1 and 8.1 p.p.m. of the 2-alkylquinoline type.

A likely mechanism for this reaction involves initial acid-catalyzed fragmentation of the *t*-butyl ester **1** forming 2-quinolylacetonitrile (**10**), carbon dioxide, and the *t*-butyl cation. The product **11** is formed by recombination of the nitrile and the carbonium ion in a Ritter reaction.[12] Hydrolysis of the *t*-butyl ester **1** in 70% sulfuric acid gave 2-quinolylacetamide (**12**)[13] in low yield. Decomposition of *t*-butyl cyano-2(1H)-1,10-phenanthrolylideneacetate (**4**) by cold hydrochloric acid furnished 2-(1,10-phenanthrolyl)acetonitrile (**13**) in good yield.



Experimental[14]

***t*-Butyl Cyano-2(1H)-quinolylideneacetate** (**1**).—Three grams (0.066 mole) of a 53% sodium hydride dispersion in mineral oil was placed in a 125-ml. three-necked flask. The mineral oil was removed by washing the dispersion three times with 20 ml. portions of dry petroleum ether. Agitation was provided by means of a magnetic stirrer. The three-necked flask was fitted with a reflux condenser, a pressure-compensated dropping funnel, and a thermometer. A three-way stopcock was connected to the top of the condenser and attached to a nitrogen tank and a water aspirator. Any residual petroleum ether then was removed by alternately evacuating the system and flushing with nitrogen. The aspirator was removed, but nitrogen sweeping was continued during the course of the reaction. Anhydrous dimethylformamide (DMF) (20 ml.) was added through the dropping funnel. The reaction flask was placed in an ice bath while 8.4 g. (0.06 mole) of *t*-butyl cyanoacetate was added dropwise. Upon completion of the addition, the ice bath was removed and replaced with an electrically heated oil bath. The mixture was heated to 50° and 4.9 g. (0.03 mole) of 2-chloroquinoline in 5 ml. of DMF was added dropwise. The reaction temperature was raised slowly to 120° and maintained at this temperature for 4.5 hr. The mixture then was cooled to 80° and 5 ml. of water added. The mixture was cooled to room temperature, transferred to a one-necked flask, and the excess DMF was removed by means of a rotary evaporator. The residue was added to 300 ml. of water. The resulting yellow precipitate was collected by suction filtration, washed with water, and dried to give 6.1 g. (76%) of crude product, m.p. 185–188°. Crystallization from dioxane gave fine yellow needles, m.p. 203°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.62; H, 5.91; N, 10.33.

Ethyl Cyano-2(1H)-quinolylideneacetate (**2**).—The procedure was similar to that used for the preparation of *t*-butyl cyano-2-(1H)-quinolylideneacetate except 6.80 g. (0.06 mole) of ethyl cyanoacetate was substituted for *t*-butyl cyanoacetate. Crystallization of the crude reaction product from a chloroform–ether mixture gave 4.82 g. (74%) of yellow crystals, m.p. 163–164°.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.03; N, 11.66. Found: C, 69.89; H, 5.40; N, 11.56.

2(1H)-Quinolylidenemalononitrile (**3**).—The procedure was similar to that used to prepare *t*-butyl cyano-2(1H)-quinolyl-

(12) R. C. Fuson, "Reactions of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1962, p. 156.

(13) F. Zymalkowski and W. Schauer, *Arch. Pharm.*, **290**, 218 (1957); *Chem. Abstr.*, **51**, 16472*b* (1957).

(14) Melting points are uncorrected. Elemental analyses were by Dr. Alfred Bernhardt, Mülheim, Germany, and Dr. F. Pascher, Bonn, Germany. Infrared spectra were obtained on a Beckman IR-7 spectrometer and a Perkin-Elmer Infracord. Ultraviolet and visible spectra were obtained on a Bausch and Lomb Spectronic 505 and n.m.r. spectra were determined on a Varian A-60 spectrometer. The n.m.r. spectra are reported as parts per million from tetramethylsilane.

ideneacetate except 4.0 g. (0.06 mole) of malononitrile in 8 ml. of DMF was substituted for *t*-butyl cyanoacetate. In addition it was necessary to adjust the pH of the aqueous work-up to 7 with concentrated hydrochloric acid to effect precipitation. The crude yellow product weighed 4.3 g. (74%) and melted at 288–292°. Recrystallization from dioxane gave fine yellow needles, m.p. 300–301°

Anal. Calcd. for $C_{12}H_7N_3$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.61; H, 3.47; N, 21.94.

***t*-Butyl Cyano-2(1H)-1,10-phenanthrolylideneacetate (4).**—The procedure was similar to that used for the preparation of *t*-butyl cyano-2-(1H)-quinolylideneacetate except the molar quantities were reduced. One and one-half grams (0.033 mole) of 53% sodium hydride dispersion was used. After removal of the mineral oil, 10 ml. of DMF was added. To the cooled sodium hydride–DMF dispersion was added 4.2 g. (0.03 mole) of *t*-butyl cyanoacetate dropwise. After the addition, the temperature was raised to 50° and 3.5 g. (0.0163 mole) of 2-chloro-1,10-phenanthroline[15] in 13 ml. of DMF was added dropwise. The reaction time, temperature, and work-up were the same as for *t*-butyl cyano-2(1H)-quinolylideneacetate. The precipitated product was recrystallized from dioxane to furnish 3.25 g. (62%) of yellow crystals, m.p. 225–228°. Further recrystallization raised the melting point to 228–229°.

Anal. Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.36; N, 13.16. Found: C, 71.59; H, 5.43; N, 13.01.

2-Quinolyl-2(1H)-quinolylideneacetonitrile (8).[10]—The procedure was similar to the preparation of *t*-butyl cyano-2(1H)-quinolylideneacetate except 5.1 g. (0.06 mole) of cyanoacetamide in 15 ml. of DMF was substituted for *t*-butyl cyanoacetate. After the aqueous work-up, the precipitated product was collected by suction filtration and washed with acetone to furnish 1.5 g. (34%) of 2-quinolyl-2(1H)-quinolylideneacetonitrile, m.p. 272–277°. Recrystallization from dioxane raised the melting point to 284°.

Anal. Calcd. for $C_{20}H_{13}N_3$: C, 81.33; H, 4.45; N, 14.32. Found: C, 80.84; H, 4.37; N, 14.43.

The filtrate from the aqueous work-up was concentrated on the rotary evaporator to give a solid which was washed with ethanol. The solid was determined to be crude sodium cyanate from its infrared and X-ray powder diffraction spectra and also by its reaction with mineral acids to give carbon dioxide and ammonium ion.

Cyano-2(1H)-quinolylideneacetamide (6).—The same molar quantities were used as in the preparation of 2-quinolyl-2(1H)-quinolylideneacetonitrile. However, the reaction was carried out at 50° for only 1 hr. and stopped by the addition of 5 ml. of water. The reaction mixture was transferred to a one-necked flask and the excess DMF was removed on a rotary evaporator. To the residue was added 100 ml. of water to give an oily yellow precipitate which solidified upon cooling in an ice bath. The precipitate was collected by suction filtration and extracted with several 20-ml. portions of benzene. Evaporation of the combined benzene extracts yielded 2.16 g. of 2-chloroquinoline identified by comparison of its infrared spectrum with an authentic sample. The benzene-insoluble residue was washed with hot water. Recrystallization from DMF yielded 0.26 g. of yellow crystals, m.p. 246–251°. Further recrystallization raised the melting point to 252–253°.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.30; N, 19.90. Found: C, 68.24; H, 4.28; N, 20.08.

2-Quinolyl-N-*t*-butylacetamide (11).—One gram (0.00374 mole) of *t*-butyl cyano-2(1H)-quinolylideneacetate was dissolved in 10 ml. of glacial acetic acid by heating on the steam bath. To the warm solution was added dropwise 0.5 ml. of fuming (30–33%) sulfuric acid. The solution became dark red in color. The mixture was heated on the steam bath for 15 min., cooled, and poured onto 30 g. of ice. Neutralization with ammonium hydroxide gave a cream-colored solid. The solid was collected by suction filtration and dried to give 0.562 g. (62%) of product, m.p. 152–154°. Recrystallization from ethanol–water raised the melting point to 157–158°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.34; H, 7.49; N, 11.57. Found: C, 74.29; H, 7.58; N, 11.71.

2-Quinolylacetamide (12).[13]—One gram (0.00374 mole) of *t*-butyl cyano-2(1H)-quinolylideneacetate was added to 7 ml. of 70% sulfuric acid. Gas evolution occurred upon the addition and the solution became dark red in color. The mixture was heated on an oil bath at 75° for 1 hr., cooled, and poured onto 20 g. of ice. Neutralization with ammonium hydroxide gave 0.169 g. of light tan solid, m.p. 184–187°. The aqueous filtrate was extracted with chloroform. Evaporation of the chloroform extracts gave an additional 0.048 g. of light tan solid, m.p. 179–185°. The over-all yield was 0.217 g. (31%). Recrystallization from water raised the melting point to 187–189°.

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.80; H, 5.30; N, 15.20.

2-(1,10-Phenanthrolyl)acetonitrile (13).—A flask containing 6 ml. of concentrated hydrochloric acid was cooled in an ice bath and magnetically stirred while 0.800 g. of *t*-butyl cyano-2-(1H)-1,10-phenanthrolylideneacetate was added portionwise. Upon completion of the addition, the solution was stirred for 10 min. at room temperature. The color of the solution changed from dark orange to pale yellow and gas evolution occurred. The solution was poured into 30 ml. of ice–water and neutralized with ammonium hydroxide. The precipitate was collected by suction filtration and dried to furnish 0.536 g. (97%) of product, m.p. 180.5–183°. Recrystallization from aqueous DMF gave cream-colored needles, m.p. 185–186°. The infrared spectrum shows nitrile absorption at 2230 $cm.^{-1}$.

Anal. Calcd. for $C_{14}H_9N_3$: C, 76.70; H, 4.14; N, 19.17. Found: C, 76.43; H, 4.37; N, 19.18.

Acknowledgment.—We are indebted to Professor E. J. Corey of Harvard University for the determination of the n.m.r. spectra, and for helpful discussions. We also thank Professor L. L. Pytlewski of Drexel Institute of Technology for the determination of the X-ray diffraction spectrum of the crude sodium cyanate.

(15) B. E. Halcrow and W. O. Kermack, *J. Chem. Soc.*, **1946**, 155.