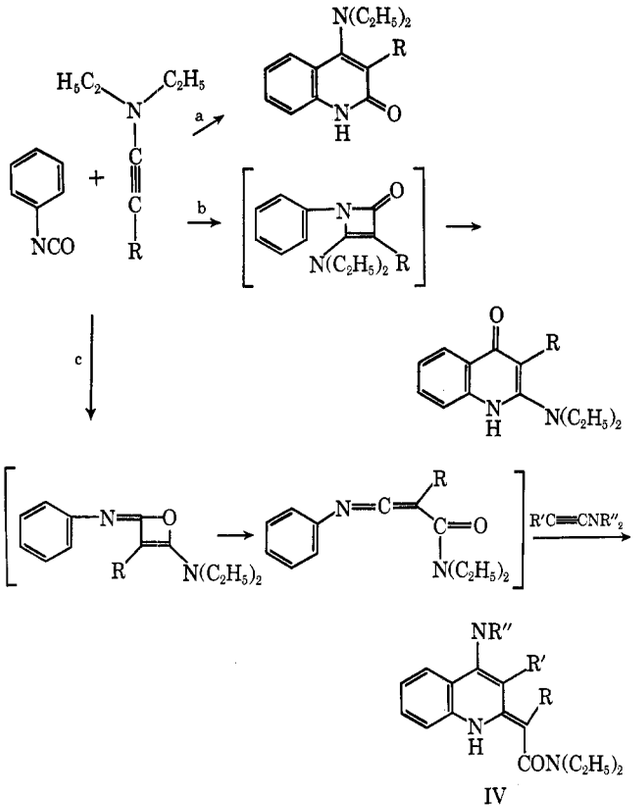
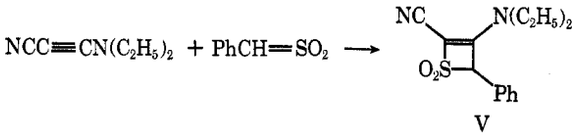


converted to all three product types, could not yet be ruled out rigorously.

The cyanoynamine I reacted with phenylsulfene to give a four-membered cyclic sulfone V in analogy to other ynamines reported[1] previously.



Experimental Section

Preparation of *N*,*N*-Diethylcyanoethynylamine (I).—A solution of 36.5 ml of 1.6 *M* *n*-butyllithium in hexane (58.5 mmol) diluted with 10 ml of dry ether was slowly added to 5.8 g (28.6 mmol) of *N*,*N*-diethyl-1,2,2-trichlorovinylamine at −20°. After stirring at room temperature for 45 min the mixture was cooled again to −20° and 1.75 g (28.6 mmol) of cyanogen chloride in 5 ml of dry ether was added slowly. The mixture was stirred for 45 min at room temperature and centrifuged. Evaporation of the supernatant and two ether washes of the precipitated lithium chloride gave a thick liquid which was distilled. The ynamine was collected in Dry Ice, bp 45–55° (0.04 mm). After two distillations 2.10 g (63%) of the ynamine was collected: bp 47° (0.05 mm); ν_{max}^{neat} 2945, 2210, 2135, 1432 cm^{-1}; nmr ($CDCl_3$ with TMS) δ 1.24 (t, 3 H), 3.13 (q, 2 H); uv λ_{max}^{hexane} 221, 232, 242 (ϵ 5.85 × 10^5), 254 mμ.

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.59; H, 8.27; N, 22.75.

Reaction of *N*,*N*-Diethylcyanoethynylamine with Phenylsulfene.—Benzylsulfonyl chloride, 0.932 g (4.91 mmol), suspended in 5 ml of benzene was added to a solution of 0.6 g (4.91 mmol) of the cyanoynamine and 0.6 g (5.95 mmol) of triethylamine in 15 ml of dry benzene. The solution was stirred for 18 hr and the precipitated triethylamine hydrochloride was filtered. The collected filtrate was vacuum evaporated to a thick oil which crystallized from ethyl acetate. Recrystallization from isopropyl alcohol gave 0.132 g (9.8%) of the 1:1 adduct V, mp 194–195°. Reactions in tetrahydrafuran and dichloromethane at −30° for 1 hr and subsequently at 0° for 48 hr did not give improved yields of the adduct, nor could other products be identified.

Spectral data follow: ν_{max}^{KBr} 2190, 1600, 1580, 1512, 1308, 1160, 1120 cm^{-1}; nmr (DMSO-d_6 with TMS) δ 1.12 (t, 6 H), 3.53 (q, 4 H), 4.61 (s, 1 H), 7.50 (s, 5 H); uv λ_{max}^{EtOH} 223, 283, 344 mμ.

Anal. Calcd for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.84; N, 10.14; S, 11.58. Found: C, 60.93; H, 5.68; N, 10.10; S, 11.69.

Reaction of *N*,*N*-Diethylcyanoethynylamine with Phenyl Isocyanate.—A solution of 0.840 g (7.85 mmol) of phenyl isocyanate in 5 ml of dry acetonitrile or benzene was added to 0.862 g (7.12 mmol) of the ynamine I at room temperature. The solution was stirred for 60 hr under nitrogen, and the precipitated 2-amino-4-quinolone was filtered and washed with ethanol, yielding 60 mg (7.1%) of white needles: mp 297–298° dec; ν_{max}^{KBr} 2940, 2200, 1627, 1613, 1580, 1333 cm^{-1}; nmr (HMPA) sharp NH singlet at δ 8.75; uv $\lambda_{max}^{Ethanol}$ 243, 260, 308 mμ.

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.27; N, 17.42. Found: C, 69.88; H, 6.36; N, 17.16.

Changing solvent from acetonitrile to benzene did not affect this reaction and no 4-amino-2-quinolone could be obtained even when a dilute solution of ynamine (0.5 g in 10 ml) was added to a twofold excess of phenyl isocyanate in benzene or acetonitrile over a period of 7 hr. Evaporation of the filtrate and chromatography on a column of Woelm silica gel (activity I) in methylene chloride and ethanol (0.5%) gave a yellow solid, 0.592 g (46%), which was recrystallized from ethyl acetate to mp 135–136° and distilled at block temperature 170° (0.001 mm). This product is the 2:1 adduct IV by the following data: ν_{max}^{KBr} 3420, 2950, 2910, 2205, 2180, 1612, 1600, 1562, 1552 cm^{-1}; nmr ($CDCl_3$ with TMS) δ 1.29 (t, 12 H), 3.6 (q), 3.8 (q) (total 8 H), 7.6 (m, 4 H), 15.0 (s, 1 H); uv ν_{max}^{EtOH} 230, 243, 264, 333 mμ; the 333-mμ absorption shifted to 353 mμ in base and returned to 333 mμ upon acidification; major mass spectrum peaks *m/e* (rel intensity) 363 (10), 348 (10), 334 (10), 266 (10), 239 (10), 100 (100), 72 (40), 44 (10), 29 (20).

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 69.38; H, 6.93; N, 19.27. Found: C, 69.21; H, 7.04; N, 19.49.

A reaction in tetrahydrofuran at −30° for 1 hr and 0° for 48 hr gave a 17% yield of the 2:1 adduct. No other products or intermediates could be identified. Attempted reactions of 4-*N*,*N*-diethylamino-3-phenyl-2-quinolone with *N*,*N*-diethylcyanoethynylamine.

Addition of the cyanoynamine I to the 3-phenyl- (or 3-carbethoxy-) 4-amino-2-quinolone in either hexamethylphosphotriamide or acetonitrile for 36 hr yielded only starting materials by tlc and ir.

Registry No.—I, 26391-04-8; IV, 34281-05-5; V, 34281-06-6; phenyl isocyanate, 1122-85-6; phenylsulfene, 17346-42-8; 2-amino-4-quinolone, 34281-08-8.

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A Facile Method for N-Acylation of Ring Activated Phenylhydroxylamines

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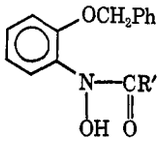
During a study of methods for the preparation of structural analogs of 2,4-dihydroxy-1,4-benzoxazin-3-one,[2] it was found that the acylation of *o*-methoxy-

(1) Taken in part from the dissertation presented by M. D. Corbett, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) E. E. Smissman and M. D. Corbett, *J. Org. Chem.*, **37**, 1704 (1972).

TABLE I

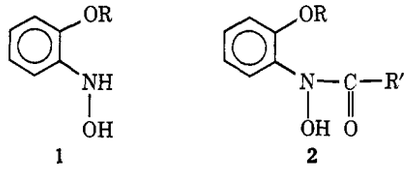
HYDROXAMIC ACIDS (2b) OBTAINED BY THE ACYLATION OF *o*-BENZYLOXYPHENYLHYDROXYLAMINE (1b)



Acyl halide	Registry no.	R′	Yield,[a] %	Mp, °C (crystn solvent)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
$Cl_2CH(C{=}O)Cl$	34287-98-4	$CHCl_2$	66	124–126 (C_6H_6)	55.25	4.02	4.29	55.62	3.76	4.30
$Cl_2CH(C{=}O)Cl$	34287-99-5	CH_2Cl	82	99–101 (Et_2O)	61.76	4.84	4.80	62.06	4.92	4.74
$BrCH(C{=}O)Cl$	34288-00-1	CH_2Br	87	96–98 (Me_2CO–Et_2O)	53.59	4.20	4.17	53.84	4.21	4.26
$CH_3CHBr(C{=}O)Cl$	34288-01-2	$CHBrCH_3$	79	125–127 (Et_2O)	54.87	4.60	4.00	54.91	4.88	4.05
$Ph(CHBr(C{=}O)Cl$	34288-02-3	PhCHBr	67	115–117 (Me_2CO–Et_2O)	61.19	4.40	3.40	61.43	4.51	3.38
$EtOC{=}O(C{=}O)Cl$	34288-03-4	O=COEt	69	Oil						

[a] Yields are for purified products, except for 6.

methoxy- and *o*-benzyloxyphenylhydroxylamines (**1a,b**) proceeded in very low yields with the formation of large amounts of tarry materials. This was assumed to be due to the occurrence of the Bamberger rearrangement[3] which explains the sensitivity of phenylhydroxylamines to acidic reagents. The acylation of **1a** and **1b**



1 **2**

a, R = OCH_2OCH_3
b, R = $OCH_2C_6H_5$

with dichloroacetyl chloride under anhydrous conditions gave the corresponding hydroxamic acids **2** in yields of less than 10%. The addition of organic bases or sodium bicarbonate to neutralize the hydrochloric acid which is liberated failed to increase the yield. The use of dicyclohexylcarbodiimide and free organic acids[4] increased the yield of some hydroxamic acid products to about 30% but was found to be inapplicable for organic acids substituted on the α carbon with strongly electron-withdrawing groups. Even under relatively neutral conditions the Bamberger and related rearrangements[5,6] proceed with ring-activated phenylhydroxylamines.

The acylation of phenylhydroxylamine with long-chain aliphatic acid chlorides was reported[7] to give high yields of the desired hydroxamic acids when an aqueous solution of sodium bicarbonate was suspended in an ether solution of the reactants. This method was successfully extended to the acylation of the activated hydroxylamines **1** with highly reactive acid chlorides. Table I lists the products and yields obtained utilizing this process with *o*-benzyloxyphenylhydroxylamine. The spectra of all compounds are consistent with the assigned structures.

(3) H. J. Shine, "Aromatic Rearrangements," Monograph 6 of "Reaction Mechanisms in Organic Chemistry," C. Eaborn and N. B. Chapman, Ed., Elsevier, New York, N. Y., 1967.

(4) M. T. W. Hearn and A. D. Ward, *Aust. J. Chem.*, **22**, 1731 (1969).

(5) R. T. Coutts and N. J. Pound, *Can. J. Chem.*, **48**, 1859 (1970).

(6) G. T. Tisue, M. Grassmann, and W. Lwowski, *Tetrahedron*, **24**, 999 (1968).

(7) V. K. Gupta and S. G. Tandon, *J. Indian. Chem. Soc.*, **46**, 831 (1969).

Experimental Section[8]

***o*-(Benzyloxy)nitrobenzene**.—To potassium *o*-nitrophenoxide (35.4 g, 0.20 mol) dissolved in 300 ml of DMF was added benzyl bromide (34.2 g, 0.20 mol) in 15 min. The mixture was stirred for 40 min, combined with 200 ml of C_6H_6 and 200 ml of H_2O, and shaken. The aqueous layer was extracted with 200 ml of C_6H_6 after adding 300 ml of H_2O. The combined C_6H_6 fractions were washed with 200 ml of 5% NaOH, 200 ml of H_2O, and 100 ml of saturated NaCl. The C_6H_6 solution was dried (Na_2SO_4) and the solvent was removed *in vacuo* to give an orange oil, which was distilled at 127–129° (0.05 mm) to give 29.8 g (65%) of a pale yellow liquid; spectral data are consistent with the assigned structure.

***o*-(Benzyloxy)phenylhydroxylamine (1b)**.—*o*-(Benzyloxy)nitrobenzene (55.2 g, 0.24 mol) and NH_4Cl (24.0 g, 0.44 mol) in 600 ml of 60% EtOH were stirred vigorously while Zn dust (24.0 g, 0.37 g-atom) was added in small portions in the course of 20 min. The mixture was stirred for an additional 15 min, after which 200 ml of H_2O was added and the suspension was filtered. The filter cake was washed with 200 ml of C_6H_6, and the filtrates were combined and shaken. The aqueous portion was diluted with 200 ml of H_2O and extracted with 200 ml of C_6H_6. The combined C_6H_6 fractions were washed with 100 ml of H_2O and 50 ml of saturated NaCl and dried (Na_2SO_4), and the solvent was reduced in volume *in vacuo* to about 300 ml. This solution was treated with petroleum ether (bp 60–80°) until the cloud point was attained. The opaque solution was stirred until a flocculent white solid formed. An additional 200 ml of petroleum ether (bp 60–68°) was added and the mixture was cooled in an ice bath. The solid was collected by filtration and washed with 200 ml of petroleum ether (bp 60–68°). The solid was dried at room temperature to give 26.0 g (50%) of white solid, mp 73–76°; a dark red color developed with alkaline 2,3,5-triphenyltetrazolium chloride;[9] spectral data are consistent with the assigned structures. Compound **1b** could be stored for several days at 5° with little decomposition.

Acylation of *o*-(Benzyloxy)phenylhydroxylamine (1b).—Equimolar quantities of **1b** and the acid chloride must be used to minimize the formation of side products. The purified products can be obtained by crystallization (Table I). A typical procedure follows.

***N*-[*o*-(Benzyloxy)phenyl]-2,2-dichloroacetohydroxamic Acid**.—*o*-(Benzyloxy)phenylhydroxylamine (6.5 g, 0.03 mol) dissolved in 100 ml of Et_2O was placed in a 300-ml flask with $NaHCO_3$ (2.8 g, 0.034 mol) in 12 ml of H_2O. The mixture was cooled to −5° by means of an ice–salt bath and stirred vigorously while dichloroacetyl chloride (4.5 g, 0.03 mol) in 20 ml of anhydrous Et_2O was added dropwise in the course of 30 min. The pale yellow suspension was stirred and cooled for an additional 15 min, after which it was combined with 50 ml of Et_2O and washed twice with 50 ml of H_2O. The ethereal solution was combined

(8) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR-10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N Analyzer, University of Kansas.

(9) G. A. Snow, *J. Chem. Soc.*, 258 (1954).

with 30 ml of C_6H_6 and dried (Na_2SO_4). Removal of the solvent produced a solid which was recrystallized twice (C_6H_6) to give 6.5 g (66%) of white crystals, mp 124.0–126°, violet color with $FeCl_3$ in EtOH; spectral data are consistent with the structure assigned.

Anal. Calcd for $C_{15}H_{13}NO_3Cl_2$: C, 55.24; H, 4.02; N, 4.29. Found: C, 55.62; H, 3.76; N, 4.30.

Registry No.—**1b**, 34288-04-5; *o*-(benzyloxy)nitrobenzene, 4560-41-2.

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Synthesis of 3-Chloroquinolines from Indoles and Thermally Generated Dichlorocarbenes

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The reported conversion of pyrrole to 2- and 3-chloropyridines on reaction with thermally generated dichlorocarbene[1] suggested that the reaction could be utilized in an analogous synthesis of chloroquinolines. Recently, Baker, *et al.*,[2] found that improved conversions of pyrrole to the 2- and 3-chloropyridine mixture (86% yields from a 550° pyrolysis) could be obtained with the use of a preheater (at 250°) and stated that the reaction could be extended to other five-membered ring heterocycles, methylpyrrole, and indole, although details for these latter conversions were not given.

We report here the results of experiments using thermally generated dichlorocarbene in the synthesis of 3-chloroquinoline, 3-chloroquinaldine, 3-chlorolepidine, and 3-chloro-2,4-dimethylquinoline from the appropriately substituted indole (see Table I). Syntheses of substituted chloroquinolines by a modified Reimer–Tieman procedure have been reported[3] with yields generally around 10%. The advantages of the thermal method reported here are improved yields, fewer side-reaction products, and facile isolation by column chromatography.

The effects of variations in reaction parameters on the yields of chloroquinolines were investigated briefly. In the formation of 2-chloroquinoline from indole an increase in the pyrolysis temperature resulted in a slight increase in the yield of the 2-chloroquinoline coproduct. Faster nitrogen carrier gas flow rates (from 100 to 200 ml/min) produced larger yields of 2-chloroquinoline (from indole) and smaller yields of 3-chloroquinaldine (from 2-methylindole). Decreases in the chloroform–indole ratio lowered the yield of the chloroquinoline products (a decrease of 10 and 17% in the indole and 2-methylindole experiments, respectively).

Other dichlorocarbene precursors such as carbon tetrachloride, ethyl trichloroacetate, and sodium trichloroacetate produced lower yields (1–20% of chloroquinoline product).

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infared spectra were measured on a Beckman IR-8 spectrophotometer, ultraviolet spectra were measured on a Perkin-Elmer Model 202 spectrophotometer, and nmr spectra were measured on a Varian T-60 spectrometer.

Glpc analyses and preparative scale separations were made on an F & M Model 810 gas chromatograph using an 8 ft × 0.375 in. 25% SE-30 column heated to 100° for 7 min and then programmed at 2°/min to 250°. In the glpc analyses naphthalene was used as an internal standard.

The pyrolyses were carried out at 550° in the appratus previously described.[4] In the present experiments the pyrolysis zone (*ca.* 20 cm long) consisted of the unpacked Vycor tube positioned in the furnace such that the temperature throughout the zone was 550°. The region in the pyrolysis tube 15 cm above the pyrolysis zone served as a "preheater" and contained 20 ml of Berl saddles. The temperature of the "preheater" zone was 250°.

In a typical pyrolysis, the solution of the indole (0.01 mol) in the chloroform (0.05 mol) was introduced at a constant rate of 4 ml/hr into the preheater zone using a syringe and syringe drive. Nitrogen at a flow rate of 100 ml/min was used to sweep the volatilized mixture into the hot zone and the pyrolyzate was condensed in traps cooled in a Dry Ice–chloroform slurry. Upon completion of the pyrolysis the reaction tube was washed with 100 ml of methanol and the washings were added to the pyrolysate.

The residue obtained after evaporation of the methanol was treated with 10% NaOH (50 ml) and the resulting mixture was

TABLE I

MAJOR QUINOLINE PRODUCTS FROM REACTION OF DICHLOROCARBENE WITH THE SUBSTITUTED INDOLES

Reactant	Quinoline	Yield, % Gc	Yield, % Isolated	Mp, °C	λ_{max}, nm	δ_{TMS}, ppm
Indole[a]	3-Cl[b,c]	38.7		120 (10 mm)[d]		
Indole[a,e]	3-Cl[c]		35.6			
2-Me indole	3-Cl-2-Me	48.5	39.5	69–70[f]	218, 235, 238, 278, 309, 323	2.77 (s, 3), 7.1–8.0 (m, 5)
3-Me indole	3-Cl-4-Me	48.6	42.4	55–55.5[g]	230, 280, 308, 323	2.60 (s, 3), 7.1–8.1 (m, 5), 8.62 (s, 1)
2,3-DiMe indole	3-Cl-2,4-diMe	39.3	26.2	74–74.5[h]	231, 236, 275, 308, 322	2.41 (s, 3), 2.63 (s, 3), 7.0–8.0 (m, 4)

[a] Nitrogen flow rate was 200 ml/min. [b] Gc analysis showed that 2–5% 2-chloroquinoline[c] was present in crude products. [c] Uv, ir, nmr, and mass spectra were identical with those obtained from authentic samples. [d] Boiling point. [e] Fivefold scale up of reactants. [f] Lit. mp 71–72°, ref 3b. [g] Lit. mp 54–55°, ref 3b. [h] Lit. mp 75°: G. Plancher and O. Carrasco, *Atti Accad. Naz. Lincei*, **13**, 632 (1904).

(1) H. L. Rice and T. E. Londergan, *J. Amer. Chem. Soc.*, **77**, 4678 (1955).

(2) F. S. Baker, R. E. Busby, M. Iqbal, J. Parrick, and C. J. G. Shaw, *Chem. Ind. (London)*, 1344 (1969).

(3) (a) H. Wynberg, *Chem. Rev.*, **60**, 169 (1960); (b) G. Magnanini, *Chem. Ber.*, **20**, 2608 (1887); (c) C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, 928 (1964).

(4) J. M. Patterson, A. Tsamasfyros, and W. T. Smith, Jr., *J. Heterocycl. Chem.*, **5**, 727 (1968).