β,β-Dichlorovinyl Ketones. II. Reactions with Aromatic Amines[2]

ROBERT L. SOULEN, DONALD G. KUNDIGER,[2a] SCOTT SEARLES, JR.,[2b] AND ROBERT A. SANCHEZ

Department of Chemistry, Kansas State University, Manhattan, Kansas

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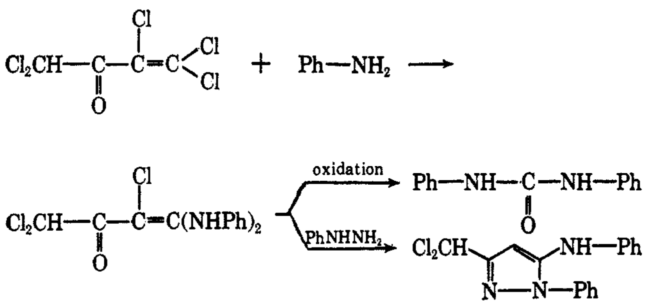
A study was made of the reactions of various β,β-dichlorovinyl ketones with aromatic amines. In general, clean disubstitution to yield β,β-dianilinovinyl ketones was observed. The dianilinovinyl ketones could be cyclized to 2-anilinoquinolines in high yields, thus providing a route to these derivatives which promises to be of synthetic utility.

The extraordinary ease of replacing β-chlorine atoms in β-chloro α,β-unsaturated carbonyl compounds has been described in recent years in an extensive series of publications, largely by Kochetkov and co-workers.[3] Although the literature on β,β-dichlorovinyl ketones is scant, these compounds, as anticipated, seem to show the same high degree of reactivity.[4-6]

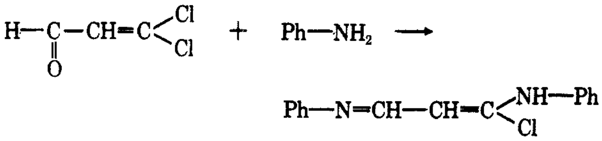
A representative example amongst several investigated by Roedig and co-workers was the reaction of 1,1,3,4,4-pentachloro-3-buten-2-one with aniline, which was formulated as giving simple substitution of the two β-chlorine atoms by anilino groups (sequence 1).[5]



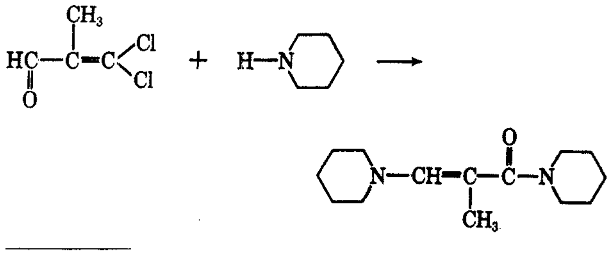
(1)

The proposed structure of the product was well supported by oxidation to *sym*-diphenylurea, and by its reactions with phenylhydrazine to form a substance corresponding to the expected 5-anilino-3-dichloromethyl-1-phenylpyrazole.

On the other hand, a different substitution pattern has been proposed for the reactions of 3,3-dichloroacrolein with aniline[7] (sequence 2) and of 3,3-dichloro-2-methylacrolein with piperidine[8] (sequence 3), as shown.



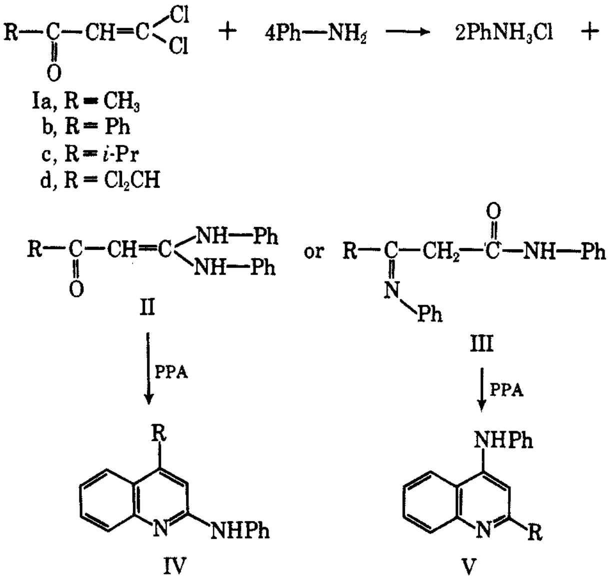
$$\mathrm{H{-}C({=}O){-}CH{=}CCl_2 + Ph{-}NH_2 \longrightarrow Ph{-}N{=}CH{-}CH{=}C(NH{-}Ph)Cl} \quad (2)$$



(3)

In view of this ambiguity, and in order to further explore the nature, utility, and generality of these types of reactions, the chemical behavior of the β,β-dichlorovinyl ketones with amines was examined in greater detail.

It was found that the reaction of 1 equiv of 4,4-dichloro-3-buten-2-one in excess aniline proceeded exothermically, yielding 2 equiv of aniline hydrochloride, and a pale yellow, crystalline solid of composition $C_{16}H_{16}N_2O$.



II

III

IV

V

(4)

The product $C_{16}H_{16}N_2O$ yielded 2 equiv of aniline upon basic aqueous hydrolysis. The carbonyl stretching frequency at 6.2 $m\mu$ and the failure to form a 2,4-dinitrophenylhydrazine derivative suggested an amide moiety (structure IIIa), although the proposed structure IIa is not excluded, since it is vinylogous to an amide.[9]

The solid in hot polyphosphoric acid (PPA) yielded a crystalline product of composition $C_{16}H_{14}N_2$, suggesting cyclization with the loss of one molecule of water. The elemental composition and infrared spectrum were consistent with a quinoline structure (IVa or Va). Both of the possible quinoline isomers have been independently synthesized and described in the

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[1] Paper I in this series: *J. Org. Chem.*, **32**, 2655 (1967). This work was supported by a grant from the Dow Chemical Co.

[2] (a) Deceased Feb 10, 1960. (b) Author to whom inquiries should be addressed: Department of Chemistry, University of Missouri, Columbia, Mo.

[3] For leading references, see (1) W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **29**, 385 (1964); (b) N. K. Kochetkov and V. N. Vinogradova, *Zh. Obshch. Khim.*, **27**, 460 (1957); *Chem. Abstr.*, **51**, 8644 (1957); (c) N. K. Kochetkov and A. N. Nesmeyanov, *Izv. Akad. Nauk, Otd. Khim. Nauk*, 949 (1957); *Chem. Abstr.*, **52**, 4603 (1958).

[4] M. Julia, *Ann. Chim.* (Paris), [12] **5**, 595 (1950).

[5] V. Roedig and H. J. Becker, *Chem. Ber.*, **89**, 1726 (1956), and references cited therein.

[6] A. N. Nesmeyanov, O. A. Reutov, and A. S. Gudkove, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 260 (1961); *Chem. Abstr.*, **55**, 23335 (1961).

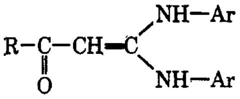
[7] A. Roedig, R. Manger, and S. Schodel, *Chem. Ber.*, **93**, 2294 (1960).

[8] D. G. Kundiger and G. F. Morris, *J. Am. Chem. Soc.*, **80**, 5988 (1958).

[9] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co. Ltd., London, 1958, pp 144, 145.

TABLE I

β,β-DIANILINOVINYL KETONES



$R{-}\underset{\underset{O}{\|}}{C}{-}CH{=}C(NH{-}Ar)_2$

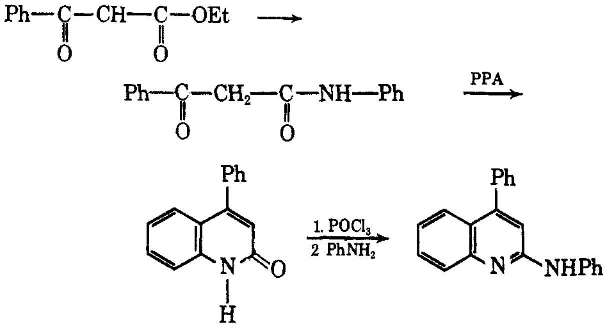
R	Ar	Registry no.	Solvent	Ratio, amine/ ketone	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Methyl	Phenyl		None[a]	7	98	116–117	76.17	6.39	11.1	76.40	6.44	10.7
Methyl	*p*-Chlorophenyl	10562-08-0	Ethanol	5	92	161–162	59.83	4.39	8.72	59.92	4.28	8.80
Phenyl	Phenyl		Benzene	6[b]	98	127–129	80.23	5.78	8.92	80.23	6.10	8.92
Isopropyl	Phenyl		Ether	5	74	102–103	77.12	7.19	9.99	77.12	7.11	9.75
Isopropyl	*o*-Tolyl	10562-09-1	Benzene	13	78	104–105	77.88	7.85	9.09	77.97	7.98	9.06
Dichloromethyl	Phenyl		Benzene	5	75	143–144	59.83	4.39	8.72	60.25	4.65	8.84

[a] When carried out in ethanol solvent and with an amine/ketone ratio of 3, the dianilinovinyl ketone was obtained in an 81% yield and had the same melting point. [b] An amine/ketone ratio of 1.0 (and the same conditions otherwise) gave a 34% yield of the same product, with no evidence for any β-anilino-β-chloroacrylophenone.

literature;[10,11] the melting point of 129–130° reported for structure IVa[10] coincided closely with that of our product (128–129°), and was clearly different from the isomer of mp 150–151°.[11]

The corresponding disubstitution and cyclization products derived from 3,3-dichloroacrylophenone (Ib) were analogous in nature, the quinoline melting at 142–143°. The isomer IVb, 2-anilino-4-phenylquinoline, has been reported once previously, when it was supposedly obtained as a very minor by-product, mp 190°, from the reaction of benzoylacetonitrile with anilinium benzenesulfonate.[12] The second possible isomer, 4-anilino-2-phenylquinoline (Vb), has been reported twice, with mp 190°[13] and 184–186°.[14]

Since the structural assignment of Hardman and Partridge[12] was not proven and since Vb seems a mechanistically possible product of their reaction, we carried out an unequivocal synthesis of 2-anilino-4-phenylquinoline (IVb) as outlined in sequence 5. The melting point of the 2-anilino-4-phenylquinoline thus obtained was 141–142° and showed no depression upon mixture with our cyclization product.



(5)

Hence, it appears well established at this point that the pathway of sequence 4a correctly applies to the β,β-dichlorovinyl ketones, as originally proposed by Roedig and Becker.[5] Extension of the reaction to other aromatic amines as well as to two other β,β-dichlorovinyl ketones, 1,1-dichloro-4-methyl-1-penten-3-one (Ic) and 1,1,4,4-tetrachloro-3-buten-2-one (Id), gave in each case an analogous substitution process, forming the appropriate β,β-bis(anilino)vinyl ketone and amine hydrochloride product. The reactions were generally carried out in benzene solution (although alcohol, ether, and excess amine were also suitable solvents) from which the amine hydrochloride precipitated in practically quantitative yields. An attempt was made to detect or isolate an intermediate monosubstitution product, from the reaction of equimolar proportions of β,β-dichloroacrylophenone and aniline at high dilution and benzene, but only the disubstitution product and recovered dichlorovinyl ketones were detectable.

As indicated in Table I, the β,β-bis(anilino)vinyl ketones were all crystalline solids, which were isolated in high yields and purity. Each was cyclized by means of polyphosphoric acid to the corresponding 2-anilinoquinoline, which was also obtained in high yield and required little purification (Table II).

The high over-all yields of most of the 2-anilinoquinolines from the dichlorovinyl ketones and the ease of each step should make this a useful synthetic method for these compounds. The only other procedure available for the synthesis of similarly substituted quinolines is a four-step synthesis described by Knorr,[10] such as was used above for the preparation of an authentic sample of 2-anilino-4-phenylquinoline.

Experimental Section

4,4-Dichloro-3-buten-2-one and **3,3-dichloroacrylophenone** were prepared as described previously.[1]

1,1-Dichloro-4-methyl-1-penten-3-one.—To a stirred solution of 88.9 g of isobutyryl chloride in 250 ml of carbon tetrachloride, maintained at −10°, 112 g of anhydrous aluminum chloride was slowly added, followed by dropwise addition of 85 g of 1,1-dichloroethylene. The temperature, which had been kept at −10° throughout this procedure, was now allowed to increase to room temperature during 2 hr with continued stirring. The reaction mixture was poured in ice–hydrochloric acid, the organic layer was separated, and the water layer was extracted twice with carbon tetrachloride. The extracts were added to the original organic layer, which was then steam distilled. The organic layer of the steam distillate was separated, dried over magnesium sulfate, and distilled to give 108 g (78%) of the title compound: bp 74–78° (14 mm), $n^{20}{}_D$ 1.4845, $d^{27}{}_4$ 1.182. (Evolution of hydrogen chloride took place during the distillation, being quite rapid when the pot temperature exceeded 80°.) The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethanol–chloroform, mp 154–155°.

Anal. Calcd for $C_{12}H_{12}Cl_2N_4O_4$: C, 41.51; H, 3.48; N, 16.14. Found: C, 41.96; H, 3.26; N, 15.65, 16.96.

1,1,4,4-Tetrachloro-3-buten-2-one.—The reaction of 130 g of dichloroacetyl chloride, 120 g of aluminum chloride, and 136.5 g of 1,1-dichloroethylene in 500 ml of carbon tetrachloride was carried by the same procedure as above, except that the tempera-

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(10) L. Knorr, *Ann.*, **236**, 103 (1886).

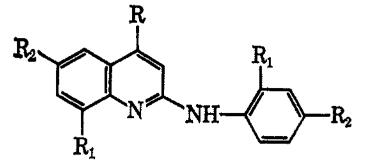
(11) M. Conrad and M. Limpach, *Ber.*, **20**, 944 (1886).

(12) R. Hardman and M. W. Partridge, *J. Chem. Soc.*, 3878 (1954).

(13) W. Dymek, *Ann. Univ. Mariae Curie-Sklodowska, Lubli-Polonia, Sect. AA*, **6** (4), 25 (1951); *Chem. Abstr.*, **49**, 1732 (1955).

(14) A. Risaliti, *Ric. Sci.*, **24**, 2531 (1954); *Chem. Abstr.*, **49**, 15902 (1955).

Table II
Substituted 2-Anilinoquinolines



R	R₁	R₂	Registry no.	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
CH_3	H	H		128–129[a]	97	82.02	6.03	11.95	81.76	5.61	11.75
C_6H_5	H	H		142–143	74	85.10	5.44	9.44	85.51	5.55	9.37
CH_3	H	Cl	10562-10-4	144–145	93	63.38	3.39	9.24	63.15	3.95	9.37
$(CH_3)_2CH$	H	H		118–119	92	82.41	6.92	10.68	82.30	6.89	10.50
$(CH_3)_2CH$	CH_3	H	10562-11-5	134–135	74	82.71	7.64	9.65	83.15	7.66	9.67
Cl_2CH	H			97–99	48	63.38	3.99	9.24	63.39	4.24	9.15

[a] Knorr[10] reported a melting point of 129–130° for 2-anilino-4-methylquinoline.

ture was maintained at 0–10° during the addition processes and the final reaction mixture was stirred for 4 hr at room temperature and then heated to 50° for a few minutes. Distillation of the steam-distilled organic product gave 12.5 g (7%) of the crude product: bp 89–93° (12 mm), n^{19}D 1.5374–1.5404. Several attempts to form a 2,4-dinitrophenylhydrazone failed, but the successful reaction with aniline to form the expected β,β-dianilinovinyl ketone (Table I) and the cyclization of the latter to the corresponding quinoline derivative (Table II) provided analyzed derivatives of this ketone.

β,β-Dianilinovinyl Ketones.—The dianilinovinyl ketones of Table I were synthesized by dropwise addition of the freshly distilled dichlorovinyl ketone to the stirred amine (neat or in solvent) at room temperature. The reactions were generally exothermic except for the synthesis with *p*-chloroaniline, which required refluxing in ethanol. The synthesis of 4,4-dianilino-3-buten-2-one (IIa) is exemplary of the procedures employed for all the compounds of Table I.

Dropwise addition of 6.9 g of 4,4-dichloro-3-buten-2-one (Ia) to 32.3 g (0.347 mole) of aniline with rapid stirring resulted in a vigorously exothermic reaction which heated the mixture to boiling (under reflux). After cooling and addition of 100 ml of ether to the mixture, stirring was continued for 14 hr. The pale yellow precipitate was filtered, dried *in vacuo*, washed with two 150-ml portions of water, and redried, to give 12.7 g (99%) of product. After recrystallization from ligroin (bp 60–70°), 12.6 g (98%) of the pure IIa was obtained as pale yellow crystals, mp 116–117.5°.

The infrared spectrum of IIa (Figure 1) provides confirmation of its structure and of the vibrational assignments previously made for 4,4-dichloro-3-buten-2-one (Ia) previously made.[1] It may be noted that the vinyl CH out-of-plane bending is at 10.38 μ, and that the C=O stretch appears as a shoulder at 6.1 μ on the apparently coincident conjugated C=C and phenyl absorption centered at 6.24 μ.

Fractional distillation of the ethereal filtrate above gave 11 g (0.12 mole) of recovered aniline, and evaporation of the aqueous filtrate from washing the original crude product gave 12.7 g (98%) of aniline hydrochloride, mp 198°.

Basic hydrolysis of a portion of IIa, followed by steam distillation, and titration of the distillate indicated that 2 equiv of aniline had formed. The product failed to form a 2,4-dinitrophenylhydrazone derivative with either phosphoric acid or sulfuric acid reagent.

Cyclization of substituted β,β-dianilinovinyl ketones to substituted 2-anilinoquinolines was carried out by the following general procedure. The β,β-dianilinovinyl ketone was stirred into ten times its weight of polyphosphoric acid and heated to 85–90° for 3 to 4 hr. The mixture was poured into water and the bright yellow precipitate was removed and dissolved in ethanol. The ethanol solution was poured into a 5% solution of potassium carbonate and the light tan precipitate was filtered and recrystallized from ethanol or benzene–ligroin (bp 60–70°) mixture.

In the case of 1,1-di(*o*-methylanilino)-4-methyl-1-buten-3-one, the reaction mixture was heated first at 110–120° for 2 hr and finally at 150° for 0.5 hr.

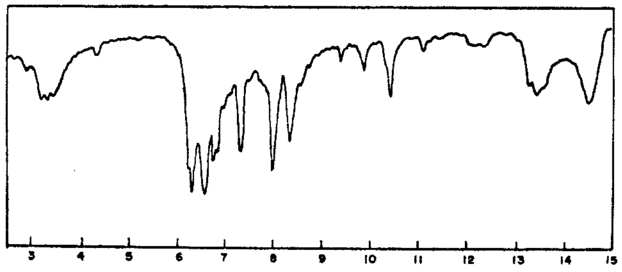


Figure 1.—Infrared spectrum of 4,4-dianilino-3-buten-2-one (IIa) (KBr wafer).

Several attempts to cause cyclization with concentrated sulfuric acid indicated that sulfonation predominates to give water- or base-soluble products.

The results of the cyclizations and the analyses of the 2-anilinoquinolines are summarized in Table II.

2-Anilino-4-phenylquinoline (IVb).—Benzoylacetanilide was prepared from ethyl benzolacetate and aniline according to the procedure of Kibler and Weissberger,[15] mp 104–105° (lit.[15] mp 104–105°).

Benzoylacetanilide was cyclized in polyphosphoric acid (120–140° for 40 min) to yield 4-phenyl-2-quinolinol in 98% yield, mp 263–263.5° (lit.[16] mp 259–260°).

4-Phenyl-2-quinolinol was heated under reflux with phosphorous oxytrichloride during 3 hr. After the usual processing and recrystallization, a 66% yield of 2-chloro-4-phenylquinoline, mp 81–87° (lit.[16] mp 87–88°), was obtained.

The crude 2-chloro-4-phenylquinoline was heated with aniline to 220°, and the cooled mixture was poured into 5% sodium hydroxide solution. The solid which formed was dissolved in ethanol and reprecipitated by again pouring into aqueous base. After filtration and crystallization from ethanol–water a 92% yield of crude 2-anilino-4-phenylquinoline was obtained, mp 134–138°. Repeated recrystallizations from benzene–ligroin and ethanol–water gave pure 2-anilino-4-phenylquinoline, mp 140–141.5°.

Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.10; H, 5.44; N, 9.44. Found: C, 84.74; H, 5.55; N, 9.32.

A mixture melting point with an equal amount of the product obtained from the cyclization of β,β-dianilinoacrylophenone gave no depression.

Registry No.—Ic, 10561-97-4; 2,4-dinitrophenylhydrazone of Ic, 10561-98-5; Id, 10561-99-6; IIa, 10562-00-2; IIb, 10562-01-3; IIc, 10562-02-4; IId, 10562-03-5; IVa, 10562-04-6; IVb, 10562-05-7; IVc, 10562-06-8; IVd, 10562-07-9.

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(15) C. J. Kibler and A. Weissberger, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 108.

(16) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).