Conversion of 2,2-Dichloroacetoacetanilides into 4-Hydroxymethyl-2(1H)-quinolones

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A novel sulfuric acid catalyzed transformation of 2,2-dichloroacetoacetanilides into 4-hydroxymethyl-2(1H)-quinolones is described; 2,2-dichlorobenzoylacetanilides gave rise to products tentatively regarded as indeno-[1,2,3-*d,e*]-2(3H)-quinolones.

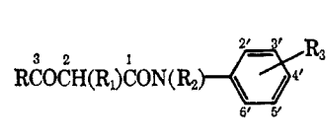
In the Knorr reaction, anilides of type **1** possessing one or two H atoms in the 2 position are converted by concentrated sulfuric acid into the corresponding 2(1H)-quinolone **2** (Chart I).[1] We now report on the cyclization of those anilides having no H atom in the 2 position, in particular, the little-known dichloro derivatives of type **3**. These substances and monochloroanilides **1** (R_1 = Cl) were readily obtained by the action of a 3:1 *M* proportion, respectively, of sulfuryl chloride on the appropriate anilide in ether.[2] Under different conditions nuclear chlorination of some substrates occurred as well. Thus, although N-ethylbenzoylacetanilide when heated with excess of sulfuryl chloride gave 2,2-dichloro-N-ethylbenzoylacetanilide (**3j**) as the final product, benzoylacetanilide on similar treatment afforded 2,2,4′-trichlorobenzoylacetanilide (**3g**). 2′,5′-Dimethylbenzoylacetanilide formed the trichloro derivative **3i** even at room temperature. Elemental and infrared analysis, supplemented on occasion by nmr spectra, served to confirm the structure of the products.

In contrast to anilides **1** (R_1 = H or Cl) which were recovered unchanged, compounds **3** were readily hydrolyzed in dilute sodium hydroxide at 20° to the corresponding 2,2-dichloroacetanilides in good yield.

Contrary to a claim[3,4] that sulfuryl chloride cyclizes acetoacetanilide at 80° into 4-methyl-2(1H)-quinolone and, furthermore, chlorsulfonates the product to yield (ultimately) 4-methyl-6-sulfamyl-2(1H)-quinolone, the reaction in our hands gave instead 2,2,4′-trichloroacetoacetanilide (**3b**). Moreover, 4-methyl-2(1H)-quinolone and sulfuryl chloride at 80° formed 3,6-dichloro-4-methyl-2(1H)-quinolone (**2b**) and not the alleged[3] 6-chlorsulfonyl derivative; in chlororoform solution the product was 3-chloro-4-methyl-2(1H)-quinolone (**2a**) converted by sulfuryl chloride into **2b.**

The effect of concentrated sulfuric acid on anilides **3** is now considered. 2,2-Dichloroacetoacetanilide (**3a**) was warmed (*ca.* 95°) with the acid for 15 min and evolved hydrogen chloride; addition of water afforded 3-chloro-4-hydroxymethyl-2(1H)-quinolone (**4b**) in 40% yield. 2,4′-Dichloro-2-methylacetoacetanilide (**5**) and sulfuric acid likewise gave (47%) 6-chloro-4-hydroxymethyl-3-methyl-2(1H)-quinolone (**4c**) and established that only one Cl atom need be available in the 2 position for this type of reaction to occur. Under similar conditions 2,2-dichloro-2′,4′,6′-trimethylacetoacetanilide (**3d**) and also compound **3h** formed little if any hydrogen chloride and were recovered unchanged; this suggested that cyclization of anilides **3a** and **5** probably was a prerequisite to hydrogen chloride production in the above instances.

CHART I



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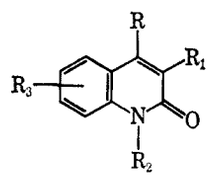
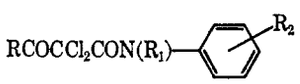
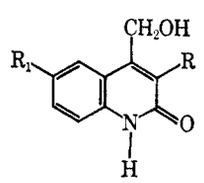


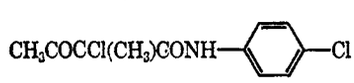
2a, R = CH_3; R_1 = Cl; R_2 = R_3 = H
b, R = CH_3; R_1 = Cl; R_2 = H; R_3 = 4′-Cl
c, R = CH_2Br; R_1 = Cl; R_2 = R_3 = H



3a, R = CH_3; R_1 = R_2 = H
b, R = CH_3; R_1 = H; R_2 = 4′-Cl
c, R = CH_3; R_1 = H; R_2 = 4′-Br
d, R = CH_3; R_1 = H; R_2 = 2′,4′,6′-$(CH_3)_3$
e, R = CH_2Br; R_1 = R_2 = H
f, R = C_6H_5; R_1 = R_2 = H
g, R = C_6H_5; R_1 = H; R_2 = 4′-Cl
h, R = C_6H_5; R_1 = H; R_2 = 2′,4′,6′-$(CH_3)_3$
i, R = C_6H_5; R_1 = H; R_2 = 4′-Cl-2′,5′-$(CH_3)_2$
j, R = C_6H_5; R_1 = C_2H_5; R_2 = H
k, R = C_6H_5; R_1 = C_2H_5; R_2 = 4′-Cl



4a, R = R_1 = H
b, R = Cl; R_1 = H
c, R = CH_3; R_1 = Cl
d, R = R_1 = Cl



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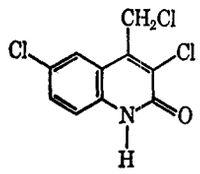
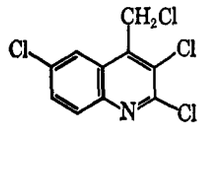
After reaction of 2,2,4′-trichloroacetoacetanilide (**3b**) with sulfuric acid, the mixture, when poured into water, furnished (22%) 4-chloromethyl-3,6-dichloro-2(1H)-quinolone (**6**) while it, when treated portionwise with water, furnished 3,6-dichloro-4-hydroxymethyl-2(1H)-quinolone (**4d**) in 77% yield, derived in part by hydrolysis of **6.** Compound **4d,** characterized also as its O-acetate and O-benzoate, gave on dehalogenation with Raney nickel and hydrogen the known[5] 4-hydroxymethyl-2(1H)-quinolone (**4a**), and with phosphorus oxychloride it formed the 4-chloromethyl derivative **6,** while, with a mixture of phosphorus oxychloride and pentachloride, the product was 4-chloromethyl-2,3,6-trichloroquinoline (**7**).

(1) "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1952, p 32.
(2) C. Bülow and E. King, *Ann.*, **439**, 211 (1924).
(3) L. Monti and S. Palmieri, *Gazz. Chim. Ital.*, **71**, 662 (1941); *Chem. Abstr.*, **37**, 128 (1943).
(4) Reference 1, p 150.
(5) T. Kametani, M. Hiiragi, and K. Kigasawa, *Yakugaku Zasshi*, **85**, 867 (1965); *Chem. Abstr.*, **64**, 5041 (1966).



6

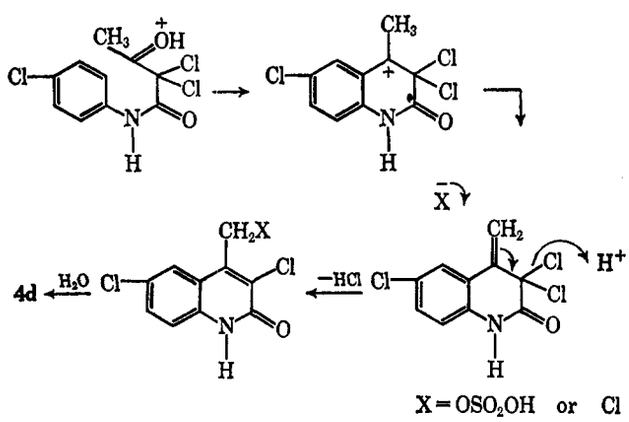


7

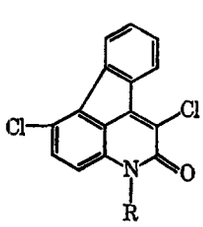
The aforementioned 4-hydroxymethyl-2(1H)-quinolone products **4** were identified by analysis and spectral data and their structures confirmed in each instance by comparison with authentic material. These reference compounds were prepared by acting on the appropriate acetoacetanilide in acetic acid with bromine, converting the resulting 4-bromo derivative **1** (R = CH_2Br) with sulfuric acid into the corresponding 4-bromomethyl-2(1H)-quinolone **2** (R = CH_2Br), and finally hydrolyzing the latter with dilute alkali.

A tentative mechanism for the anilide **3b** → quinolone **4d** conversion is outlined in Scheme I.

SCHEME I



The behavior of 2,2-dichlorobenzoylacetanilides **3** (R = C_6H_5) when allowed to react with concentrated sulfuric acid was in marked contrast to that of anilides **3** (R = CH_3). Thus, addition of the acid to 2,2,4′-trichlorobenzoylacetanilide (**3g**) resulted in a green solution which liberated hydrogen chloride (copiously) and chlorine (trace) and when poured into water afforded (60%) a yellow compound of molecular formula $C_{15}H_7Cl_2NO$. The identical product was obtained (43%) also from the 2,2-dichloroanilide **3f** and the analytical and spectral evidence available at present is consistent with structure **8a**. A similar reaction was undergone by the N-ethyl derivatives of the aforementioned two anilides, and the common product, $C_{17}H_{11}Cl_2NO$, is tentatively assigned structure **8b**. Study of this reaction and into the nature of the products is being continued.



8a, R = H
b, R = C_2H_5

Experimental Section[6]

Acetoacetanilides were prepared by rapid addition of boiling arylamine (0.1 mol) to boiling β-keto ester (0.33 mol) and refluxing the mixture for 4 min.[7] After cooling in ice, the solid material was filtered off, washed with ether, and recrystallized from aqueous alcohol. Acetoacetanilides **1** (R = CH_3, R_2 = H) obtained were (R_1, R_3 substituents, per cent yield, melting point, and analysis) H, 4′-Cl, 38%, 134–135° (lit.[8] mp 132–133°); H, 4′-Br, 38%, 137–139° (lit.[8] mp 137°); H, 2′,4′,6′-$(CH_3)_3$, 75%, 138–139° (*Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.78. Found: C, 71.06; H, 7.73); CH_3, 4′-Cl, 25%, 98–100° (*Anal.* Calcd for $C_{11}H_{12}ClNO_2$: N, 6.20. Found: N, 6.35).

Benzoylacetanilides.—Equimolar amounts of arylamine and ethyl benzoylacetate (20 g, 0.1 mol) were allowed to react at 140–145° for 1 hr.[9] Benzoylacetanilides **1** (R_1 = H) obtained were (R, R_2, R_3 substituents, per cent yield, melting point, and analysis) C_6H_5, H, 4′-Cl, 24%, 156° (lit.[10] mp 154–156°); C_6H_5, H, 2′,4′,6′-$(CH_3)_3$, 78%, 173–174° (*Anal.* Calcd for $C_{18}H_{19}NO_2$: N, 4.95. Found: N, 5.13); C_6H_5, C_2H_5, 4′-Cl, 32%, 109–110° (*Anal.* Calcd for $C_{17}H_{16}ClNO_2$: N, 4.65. Found: N, 4.60); o-$NO_2C_6H_4$, H, 4′-Cl (from ethyl o-nitrobenzoylacetate and 4-chloroaniline), 16%, 130–131° (*Anal.* Calcd for $C_{15}H_{11}ClN_2O_4$: C, 56.52; H, 3.45. Found: C, 56.72; H, 3.48); C_6H_5, H, 2′,5′-$(CH_3)_2$, 28%, 145–146° (*Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37. Found: C, 76.47; H, 6.29).

Bromination of Acetoacetanilides.[11]—A solution of bromine (9 g) in glacial acetic acid (45 ml) containing a crystal of iodine was added dropwise, over a period of 1 hr, to the anilide (0.05 mol) dissolved in glacial acetic acid (30 ml), with stirring at 20°. After a further 3 hr the mixture was poured into water, and the precipitated solid was filtered, washed with water, dried and recrystallized from benzene. 4-Bromoacetoacetanilides **1** (R = CH_2Br; R_2 = H) obtained were (R_1, R_3 substituents, per cent yield, melting point and analysis) H, H, 88%, 134–135° (lit.[11] mp 136–138°); H, 4′-Cl, 90%, 110–112° (*Anal.* Calcd for $C_{10}H_9BrClNO_2$: C, 41.31; H, 3.09. Found: C, 41.16; H, 3.13); CH_3, 4′-Cl, 81%, 109–110° (*Anal.* Calcd for $C_{11}H_{11}BrClNO_2$: C, 43.35; H, 3.62. Found: C, 43.22; H, 3.48). Similar bromination of 2,2-dichloroacetoacetanilide (**3a**) gave 4′-bromo-2,2-dichloroacetoacetanilide (**3c**), 70%, mp 71–72° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: C, 36.92; H, 2.45. Found: C, 36.90; H, 2.51) as evidenced by nmr, and alkaline hydrolysis to 4-bromoaniline. The required anilide **3e** was eventually prepared by the action of sulfuryl chloride on 4-bromoacetoacetanilide (see below).

Chlorination of Acetoacetanilides and Benzoylacetanilides with Sulfuryl Chloride. A. Introduction of One 2-Cl Atom.[2]—A solution of sulfuryl chloride (5.4 g, 0.04 mol) in dry ether (or chloroform, 5 ml) was added dropwise over 0.5 hr to the acetoacetanilide or benzoylacetanilide (0.04 mol) in dry ether (or chloroform, 25 ml) with stirring at 0°. After a further 1 hr at 20°, the solvent was removed (rotary evaporator), and the residue recrystallized from aqueous ethanol. The 2-chloro derivatives **1** (R_1 = Cl) were obtained (R, R_2, R_3 substituents, per cent yield, melting point, and analysis): CH_3, H, H, 63%, 137–139° (lit.[2] mp 137.5°); CH_3, H, 4′-Cl (chloroform), 65%, 136° (*Anal.* Calcd for $C_{10}H_9Cl_2NO_2$: N, 5.70. Found: N, 5.83); CH_2Br, H, H, 60%, 76–77° (*Anal.* Calcd for $C_{10}H_9BrClNO_2$: N, 4.82. Found: N, 4.80); CH_2Br, H, 4′-Cl, 60%, 97–98° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: N, 4.30. Found: N, 4.19); C_6H_5, H, 4′-Cl, 57%, 108–110° (*Anal.* Calcd for $C_{15}H_{11}Cl_2NO_2$: N, 4.54. Found: N, 4.61); C_6H_5, H, 4′-CH_3, 75%, 108–111° (*Anal.* Calcd for $C_{16}H_{14}ClNO_2$: N, 4.88. Found: N, 4.75); C_6H_5, C_2H_5, H, 61%, 156° (*Anal.* Calcd for $C_{17}H_{16}ClNO_2$: C, 67.77; H, 5.31. Found: C, 67.86; H, 5.43). Also obtained was **5**, 56%, 59–61° (*Anal.* Calcd for $C_{11}H_{11}Cl_2NO_2$: N, 5.38. Found: N, 5.27).

(6) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord Model 137 spectrophotometer, using 1 mg of substance per 300 mg of KBr, or a 4% solution in chloroform. Nmr spectra were measured on a Varian A-60 model. Mass spectra were recorded on a MS-9 mass spectrometer. All yields reported relate to the recrystallized material unless otherwise stated.

(7) L. Limpach, *Ber.*, **64**, 970 (1931).
(8) L. Monti and V. Cirelli, *Gazz. Chim. Ital.*, **66**, 723 (1936).
(9) B. Staskun and S. S. Israelstram, *J. Org. Chem.*, **26**, 3191 (1961).
(10) G. H. Brown, J. Figueras, R. J. Gledhill, C. J. Kibler, F. C. McCrossen, S. M. Parmerter, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.* **79**, 2919 (1957).
(11) A. K. Mallams and S. S. Israelstram, *J. Org. Chem.*, **29**, 3548 (1964).

B. Introduction of Two 2-Cl Atoms. i. Dichloroacetoacetanilides.[2]—Sulfuryl chloride (21.7 g, 0.16 mol) was added dropwise over 0.5 hr to the appropriate anilide (0.053 mol) in dry ether (50 ml) with stirring at 0°. After a further 0.5 hr the solvent and excess reagent were removed (rotary evaporator) and the residue was recrystallized from aqueous ethanol. 2,2-Dichloroacetoacetanilides **3** (R_1 = H) were obtained (R, R_2 substituents, per cent yield, melting point, and analysis): CH_3, H, 69%, 42–43° (lit.[2] mp 46–47°) (*Anal.* Calcd for $C_{10}H_9Cl_2NO_2$: N, 5.70. Found: N, 5.80); CH_3, 4′-Cl, 56%, 62–63° (lit.[2] mp 64°) (*Anal.* Calcd for $C_{10}H_8Cl_3NO_2$: N, 4.98. Found: N, 4.94); CH_2Br, H, 71%, 56–57° (*Anal.* Calcd for $C_{10}H_8BrCl_2NO_2$: C, 36.92; H, 2.45. Found: C, 37.02; H, 2.48); CH_3, 4′-Br, 55%, 71–72° (identical with the compound from **3a** and bromine); CH_3, 2′,4′,6′-$(CH_3)_3$, 74%, 97–98° (*Anal.* Calcd for $C_{13}H_{15}Cl_2NO_2$: C, 54.51; H, 5.21. Found: C, 54.33; H, 5.35).

ii. 2,2-Dichlorobenzoylacetanilides.—An excess of sulfuryl chloride (4.7 g, 0.035 mol) was added to the appropriate benzoylacetanilide (0.007 mol) at 20° and after 0.5 hr the mixture was poured into ice water, the product was filtered off, washed, and recrystallized from aqueous ethanol. Obtained in this way were the following **3** (R = C_6H_5) (R_1, R_2 substituents, per cent yield, melting point, and analysis): H, H, 77%, 136° (*Anal.* Calcd for $C_{15}H_{11}Cl_2NO_2$: Cl, 23.05; N, 4.54. Found: Cl, 22.48; N, 4.62); H, 4′-Cl (from 4′-chlorobenzoylacetanilide), 62%, 144–145° (*Anal.* Calcd for $C_{15}H_{10}Cl_3NO_2$: C, 52.55; H, 2.92; Cl, 31.04; N, 4.09. Found: C, 53.06; H, 2.97; Cl, 31.16; N, 3.90), this product resulted also (61% yield) from benzoylacetanilide and a 10 *M* amount of sulfuryl chloride refluxed for 15 min; C_2H_5, H, 64%, 98–99° (*Anal.* Calcd for $C_{17}H_{15}Cl_2NO_2$: C, 60.71; H, 4.46. Found: C, 60.72; H, 4.50); the same N-ethyl-2,2-dichloroanilide was obtained after refluxing N-ethylbenzoylacetanilide with a 8 *M* amount of sulfuryl chloride for 30 min; C_2H_5, 4′-Cl (from 4′-chloro-N-ethylbenzoylacetanilide), 75%, 97–98° (*Anal.* Calcd for $C_{17}H_{14}Cl_3NO_2$: C, 55.21; H, 3.79. Found: C, 55.00; H, 3.68); H, 4′-Cl-2′,5′-$(CH_3)_2$ (from 2′,5′-dimethylbenzoylacetanilide), 72%, 116–117° (*Anal.* Calcd for $C_{17}H_{14}Cl_2NO_2$: C, 55.24; H, 3.52. Found: C, 55.20; H, 3.71); H, 2′,4′,6′-$(CH_3)_3$, 72%, 156–158° (*Anal.* Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.71; H, 4.86. Found: C, 61.65; H, 5.06). The recrystallized anilides in i and ii gave no color with alcoholic ferric chloride.

Hydrolysis of 2,2-Dichloroacetoacetanilides to 2,2-Dichloroacetanilides.—Compound **3a** (1.0 g) was stirred with 10% sodium hydroxide (10 ml) at 20° for 10 min. Acidification with dilute acetic acid afforded insoluble material which after recrystallization from aqueous ethanol was identified as 2,2-dichloroacetanilide (0.5 g, 60%), mp 115–116° (lit.[12] mp 117°), by comparison (mixture melting point, infrared spectrum) with a sample prepared from aniline and dichloroacetic acid.[13] Similar treatment of **3b** and **3c** gave 2,2,4′-trichloroacetanilide (67%), mp 135° (lit.[14] mp 136–137°), and 4′-bromo-2,2-dichloroacetanilide (59%), mp 145–147° (lit.[12] mp 146–147°), respectively, identified by their infrared spectra.

Anilide **3c** (0.5 g) was refluxed with 10% sodium hydroxide (10 ml) for 0.5 hr. Ether extraction of the mixture provided, after evaporation of the solvent, crude 4-bromoaniline (0.2 g, 85%), mp 85–86°, identified by its infrared spectrum.

Conversion of Anilides Having One or Two 2-H Atoms into 2(1H)-Quinolones.—The appropriate acetoacetanilide or benzoylacetanilide (1 g) was treated with concentrated sulfuric acid (2 ml) and heated on the water bath (*ca.* 95°) for 1 hr after which the mixture was poured into ice–water (~20 ml) and the insoluble product recrystallized from aqueous ethanol. The 2(1H)-quinolones **2** prepared were (R, R_1, R_2, R_3 substituents, per cent yield, melting point, and analysis) CH_3, H, H, H, 85%, 216–218° (lit.[1] mp 217°); CH_3, Cl, H, H, 87%, 272–274° (lit.[2] mp 276°); CH_3, H, H, 6-Cl, 82%, 298–300° (lit.[11] mp 292–294°); CH_3, Cl, H, 6-Cl, 86%, 300–302° (*Anal.* Calcd for $C_{10}H_7Cl_2NO$: Cl, 31.10; N, 7.25. Found: Cl, 30.65; N, 7.25); CH_2Br, H, H, H, 86%, 258–260° (lit.[11] mp 262–265°); CH_2Br, Cl, H, H, 75%, 238–240° (*Anal.* Calcd for $C_{10}H_7BrClNO$: N, 5.15. Found: N, 5.01); CH_2Br, Cl, H, 6-Cl, 85%, 278–280° (*Anal.* Calcd for $C_{10}H_6BrCl_2NO$: N, 4.56. Found: N, 4.65); CH_2Br, CH_3, H, 6-Cl, 45%, 284–286° (*Anal.* Calcd for $C_{11}H_9BrClNO$: C, 46.05; H, 3.19. Found: C, 46.17; H, 3.09); C_6H_5, Cl, H, 6-Cl, 80%, 288–290° (*Anal.* Calcd for $C_{15}H_9Cl_2NO$: N, 4.81. Found: N, 4.90); C_6H_5, Cl, H, 6-CH_3, 95%, 284–288° (*Anal.* Calcd for $C_{16}H_{12}ClNO$: C, 71.26; H, 4.08. Found: C, 71.39; H, 4.12); C_6H_5, Cl, C_2H_5, H, 81%, 158–160° (*Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 72.08; H, 4.95. Found: C, 72.14; H, 4.95); C_6H_5, H, C_2H_5, 6-Cl, 75%, 102–104° (*Anal.* Calcd for $C_{17}H_{14}ClNO$: C, 72.08; H, 4.95. Found: C, 72.16; H, 4.88). After similar reaction, 2′,4′,6′-trimethylbenzoylacetanilide was recovered (50%) unchanged, as was 4′-chloro-*o*-nitrobenzoylacetanilide (50%), while 2′,4′,6′-trimethylacetoacetanilide afforded an alkali-soluble product containing S, showing no CO absorption in the infrared spectrum, and apparently derived from sulfuric acid and mesidine (*Anal.* Calcd for $C_9H_{13}NO_3S$: C, 50.2; H, 6.04; N, 6.51. Found: C, 49.88; H, 6.38; N, 6.64).

Attempted Cyclization of Acetoacetanilide with Sulfuryl Chloride.—The work of Monti and Palmieri[3] was repeated. Sulfuryl chloride (10 g, 0.07 mol) and acetoacetanilide (7 g, 0.04 mol) were heated together for 3 hr at 80°; on addition of the sulfuryl chloride, a vigorous evolution of hydrogen chloride occurred. The product was poured onto ice, treated with concentrated ammonia and the solution evaporated on a water bath. The residue was extracted with dilute ammonia and carbon dioxide passed through this solution. Under these conditions no material separated. Monti and Palmieri reported obtaining 4-methyl-6-sulfamyl-2(1H)-quinolone, mp 316–318°. However, a recognizable product was obtained, using a modified work-up procedure: after reaction of the sulfuryl chloride (10 g) and acetoacetanilide (7 g) for 3 hr at 80° as before, the mixture was poured into ice–water, whereupon an oil separated. This was extracted with ether, dried over sodium sulfate and the ether evaporated to give a yellow oil (5 g, 55%) which could not be induced to crystallize, and was identified as crude 2,2,4′-trichloroacetoacetanilide (**3b**) by its infrared spectrum.

Attempted Chlorsulfonation of 4-Methyl-2(1H)-quinolone.—Sulfuryl chloride (3 g, 0.022 mol) and 4-methyl-2(1H)-quinolone (1.9 g, 0.012 mol) were allowed to react for 3 hr at 80°;[3] addition of the sulfuryl chloride to the quinolone led to a ready evolution of hydrogen chloride. Treatment with water yielded crude 3,6-dichloro-4-methyl-2(1H)-quinolone (**2b**) which was obtained as colorless crystals (from aqueous dimethylformamide) (2 g, 77%), mp 300–301°, identified by comparison (mixture melting point, infrared spectrum) with a sample derived by cyclization of 2,4′-dichloroacetoacetanilide (see below). Monti and Palmieri[3] reported forming 6-chlorsulfonyl-4-methyl-2(1H)-quinolone.

4-Methyl-2(1H)-quinolone (1.9 g) was treated with a solution of sulfuryl chloride (3 g) in dry chloroform (50 ml) and refluxed for 20 min. Removal of the chloroform and excess reagent under reduced pressure afforded crude 3-chloro-4-methyl-2(1H)-quinolone (**2a**), colorless crystals from aqueous ethanol (1.5 g, 65%), mp 272–274° (lit.[2] mp 276°), identified by comparison with the quinolone from 2-chloroacetoacetanilide and concentrated sulfuric acid.

Compound **2a** (1.9 g) was allowed to react with sulfuryl chloride (3 g) at 80° for 3 hr; pouring into water gave the 3,6-dichloroquinolone **2b**, colorless crystals (1.8 g, 78%), mp 300–301°, from aqueous dimethylformamide.

Conversion of 2,2-Dichloroacetoacetanilides into 4-Hydroxymethyl-2(1H)-quinolones. 3-Chloro-4-hydroxymethyl-2(1H)-quinolone (4b).—Concentrated sulfuric acid (6 ml) was added to 2,2-dichloroacetoacetanilide (**3a**, 2 g) and allowed to remain at room temperature (*ca.* 20°) for 1 hr; hydrogen chloride was evolved after 20 min. Water (20 ml) was added slowly and the white solid which deposited (1.2 g, mp 40–94°) proved to be a mixture; repeated recrystallizations from aqueous ethanol failed to provide a pure compound. The crude product (0.7 g) was dissolved in pyridine (5 ml) and chromatographed on silica gel (50 g) using benzene–methanol (6:1 v/v) as eluent. Fifteen 20-ml fractions were collected, from which was recovered anilide **3a** [0.09 g, mp 41–43° (fractions 1–5)], an unidentified mixture [0.06 g, mp 220–235° (fractions 10–15)], and the main product (fractions 6–9), *viz.* 3-chloro-4-hydroxymethyl-2(1H)-quinolone (**4b**), colorless crystals from aqueous ethanol (0.40 g, 40%): mp 259–261°; ir 2.95 (OH), 3.35 (NH), and 6.02 μ (CO).

Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.41; H, 3.83. Found: C, 57.22; H, 3.92.

Reaction of anilide **3a** (1 g) with sulfuric acid (2 ml) at 95°, for 5, 15, and 60 min, led to quinolone **4b** in 10, 32 and 20% yields, respectively.

The product was identical (mixture melting point, infrared

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(13) H. W. Doughty, *J. Amer. Chem. Soc.*, **47**, 1095 (1925).

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spectrum) with **4b** derived by refluxing 4-bromomethyl-3-chloro-2(1H)-quinolone (**2c**, 0.5 g) with 10% sodium hydroxide (10 ml) for 1 hr and neutralizing the solution with dilute acetic acid; colorless crystals from aqueous ethanol (0.3 g, 75%): mp 259–261°. Reaction of 2,2-dichloro-2',4',6'-trimethylacetoacetanilide (**3d**, 2 g) with concentrated sulfuric acid (6 ml) at 95° for 1 hr, and pouring into ice–water (200 ml) led to the recovery (1.8 g, 90%) of unchanged anilide, identified by its melting point and infrared spectrum.

6-Chloro-4-hydroxymethyl-3-methyl-2(1H)-quinolone (4c).—To 2,4'-dichloro-2-methylacetoacetanilide (**5**, 2 g) was added concentrated sulfuric acid (6 ml) and the mixture heated at 95° for 0.5 hr, during which period hydrogen chloride was evolved. After cooling (to *ca.* 20°) water (20 ml) was added slowly and the precipitated solid recrystallized from aqueous pyridine: colorless crystals (0.8 g, 47%); mp 298–300°; ir 2.95 (OH), 3.33 (NH), and 6.05 μ (CO).

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.19; H, 4.48. Found: C, 59.01; H, 4.61.

The product was identical (infrared spectrum) with the 4-hydroxymethylquinolone derived (0.3 g, 77%, mp 298–300°) by hydrolysis of 4-bromomethyl-6-chloro-3-methyl-2(1H)-quinolone (0.5 g) with 10% sodium hydroxide (10 ml) as before.

4-Chloromethyl-3,6-dichloro-2(1H)-quinolone (6) and 3,6-Dichloro-4-hydroxymethyl-2(1H)-quinolone (4d).—Concentrated sulfuric acid (6 ml) was added to 2,2,4'-trichloroacetoacetanilide (**3b**, 3 g) and warmed (*ca.* 95°) for 15 min, whereupon hydrogen chloride was evolved. After cooling (to *ca.* 20°) the mixture was divided into two equal portions.

i.—One amount was poured slowly with stirring into ice–water (100 ml); the insoluble **6** was filtered off, washed, and obtained as colorless crystals (0.3 g, 22%; mp 258–260°) from aqueous ethanol, ir 3.50 (NH) and 6.00 μ (C=O).

Anal. Calcd for $C_{10}H_6Cl_3NO$: C, 46.00; H, 2.30; Cl, 40.20; mol wt, 261 (Cl = 35). Found: C, 45.89; H, 2.42; Cl, 39.22; mol wt (mass spectrometer), 261.

A 43% yield of compound **6** was obtained after reaction of anilide **3b** (1 g) with PPA (10 g) at 140° for 0.5 hr.

A mixture of **6** (0.5 g) and 60% (v/v) sulfuric acid (10 ml) was refluxed for 1 hr and poured into water; the acid-insoluble product (colorless crystals, 0.3 g, 65%, mp 310–313°, from aqueous ethanol) proved to be quinolone **4d** obtained in ii below.

ii.—Water (100 ml) was added slowly, without cooling, to the remaining portion of the reaction mixture and the insoluble material was filtered off, washed, and recrystallized from aqueous ethanol, colorless crystals (1.0 g, 77%), mp 313–315°, of 3,6-dichloro-4-hydroxymethyl-2(1H)-quinolone (**4d**), ir 3.00 (OH), 3.35 (NH), and 6.10 μ (CO) [*Anal.* Calcd for $C_{10}H_7Cl_2NO_2$: C, 49.40; H, 2.88; Cl, 29.10; mol wt, 243 (Cl = 35). Found: C, 49.20; H, 2.87; Cl, 29.12; mol wt (mass spectrometer), 243].

Yields of **4d** after 5, 10, 60 and 120 min were 50, 65, 75 and 34%, respectively. The product was identical (infrared spectrum) with that obtained (0.3 g, 75%, mp 313–315°) by alkaline hydrolysis of 4-bromomethyl-3,6-dichloro-2(1H)-quinolone (0.5 g). The **O-acetate** was prepared by addition of acetyl chloride (6 ml) over 5 min to a solution of **4d** (1 g) in dry pyridine (5 ml) stirred at 0°. After a further 10 min, the mixture was heated at 95° for 2 min and poured into ice–water (20 ml): colorless crystals (from glacial acetic acid) (0.80 g, 70%); mp 263–264°; ir 3.38 (NH), 5.75 (ester CO), and 6.0 μ (amide CO).

Anal. Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.52; H, 3.12; Cl, 24.60; mol wt, 285 (Cl = 35). Found: C, 50.43; H, 2.97; Cl, 25.12; mol wt (mass spectrometer), 285.

The **O-benzoate** was obtained from benzoyl chloride (6 ml), quinolone **4d** (1 g) and 10% sodium hydroxide (40 ml) shaken vigorously for 15 min: colorless crystals (from glacial acetic acid) (0.85 g, 60%); mp 292–294°; ir 3.37 (NH), 5.81 (ester CO), and 6.05 μ (amide CO).

Anal. Calcd for $C_{17}H_{11}Cl_2NO_3$: C, 58.88; H, 3.17; Cl, 20.90. Found: C, 58.71; H, 3.20; Cl, 20.66.

A mixture of quinolone **4d** (0.5 g) and phosphorus oxychloride (5 ml) was refluxed for 1 hr and poured into ice–water (20 ml); the insoluble product was recrystallized from aqueous ethanol to give (0.4 g, 74%; mp 258–260°) 4-chloromethyl-3,6-dichloro-2(1H)-quinolone (**6**) identified by its infrared spectrum. With added phosphorus pentachloride (1.8 g) the reaction furnished, after pouring into ice–water, crude 4-chloromethyl-2,3,6-trichloroquinoline (**7**): colorless needles from aqueous ethanol (1.0 g, 87%); mp 123°, identified by its infrared and nmr spectra.

Anal. Calcd for $C_{10}H_5Cl_4N$: C, 42.75; H, 1.78; N, 4.98. Found: C, 42.90; H, 1.90; N, 4.82.

Dehalogenation of the 3,6-dichloroquinolone **4d** (1 g) was effected by stirring its solution in ethanol (250 ml) and 10% sodium hydroxide (10 ml) with Raney nickel (~1 g) and hydrogen (160 psi) at 20° for 8 hr. The filtered solution was evaporated to dryness and the residue extracted with absolute alcohol (20 ml). Removal of the solvent afforded 4-hydroxymethyl-2(1H)-quinolone (**4a**), colorless crystals from aqueous ethanol (0.5 g, 70%), mp 272–274° (lit.[5] mp 274–276°), identified by comparison (infrared spectrum) with the product of alkaline hydrolysis of 4-bromomethyl-2(1H)-quinolone.

Action of Sulfuric Acid on 2,2,4'-Trichlorobenzoylacetanilide (3g).—Concentrated sulfuric acid (6 ml) was added to the anilide (3 g) and the mixture heated on the water bath (*ca.* 95°) for 15 min. On addition of the acid, a light yellow color appeared, and after 1 min at 20° the solution was dark green; heating at 95° for about 5 min led to the evolution of hydrogen chloride and a trace of chlorine (detected by starch–potassium iodide paper). The brown solution was cooled and poured into ice–water (200 ml) to deposit a yellow solid which was recrystallized from aqueous pyridine to afford **8a** as yellow crystals (1.5 g, 60%): mp >350°; ir 3.60 (NH), and 6.10 μ (amide CO).

Anal. Calcd for $C_{15}H_7Cl_2NO$: C, 62.72; H, 2.42; N, 4.88; Cl, 24.80; mol wt, 287 (Cl = 35). Found: C, 62.77; H, 2.49; N, 4.96; Cl, 24.84; mol wt (mass spectrometer), 287.

The identical yellow product (as evidenced by analysis, infrared and mass spectra) was obtained (43% yield) from 2,2-dichlorobenzoylacetanilide (**3f**, 3 g) and concentrated sulfuric acid (6 ml) at 95° for 15 min.

Action of Sulfuric Acid on 2,2,4'-Trichloro-N-ethylbenzoylacetanilide (3k).—The anilide (2 g) and concentrated sulfuric acid (5 ml) were heated at 95° for 15 min; a green solution formed initially and hydrogen chloride and chlorine were subsequently evolved. After cooling and pouring into ice–water (100 ml), the insoluble yelow product (of possible structure **8b**) was recrystallized from aqueous pyridine: yellow crystals (1.4 g 82%), mp 198–201°; ir (NH absent) 6.10 μ (amide CO).

Anal. Calcd for $C_{17}H_{11}Cl_2NO$: C, 64.76; H, 3.49; mol wt, 315 (Cl = 35). Found: C, 64.93; H, 3.59; mol wt (mass spectrometer), 315.

The identical product (mixture melting point, infrared spectrum) was isolated (32% yield) after reaction of 2,2-dichloro-N-ethylbenzoylacetanilide (**3j**, 1 g) and concentrated sulfuric acid (3 ml) at 95° for 10 min.

2,2-Dichloro-2',4',6'-trimethylbenzoylacetanilide (**3h**, 1 g) and concentrated sulfuric acid (3 ml) were warmed (95°) for 1 hr; unlike the previous instances, the solution developed no green color and little, if any, hydrogen chloride was evolved. After pouring into water, unchanged anilide (0.5 g, 50%) identified by its melting point and infrared spectrum was recovered.

Registry No.—Acetoacetanitide **1** R = CH_3, R_2 = H, R_1 = H, R_3 = 2',4',6'-$(CH_3)_3$, 19359-16-1; **1** R = CH_3, R_2 = H, R_1 = CH_3, R_3 = 4'-Cl, 19359-17-2; benzoylacetanilide **1** R_1 = H, R = C_6H_5, R_2 = H, R_3 = 2',4',6'-$(CH_3)_3$, 19359-18-3; **1** R_1 = H, R = C_6H_5, R_2 = C_2H_5, R_3 = 4'-Cl, 19359-19-4; **1** R_1 = H, R = *o*-$NO_2C_6H_4$, R_2 = H, R_3 = 4'-Cl, 19359-20-7; **1** (R_1 = H), R = C_6H_5, R_2 = H, R_3 = 2',5'-$(CH_3)_2$, 19359-21-8; 4-bromoacetoacetanilide **1** (R = CH_2Br, R_2 = H), R_1 = H, R_3 = 4'-Cl, 19359-22-9; **1** (R = CH_2Br, R_2 = H), R_1 = CH_3, R_3 = 4'-Cl, 19359-23-0; 2-chloro derivative **1** (R_1 = Cl), R = CH_2Br, R_2 = H, R_3 = 4'-Cl, 19359-24-1; **1** (R_1 = Cl), R = C_6H_5, R_2 = H, R_3 = 4'-Cl, 19359-25-2; **1** (R_1 = Cl), R = C_6H_5, R_2 = H, R_3 = 4'-CH_3, 19359-26-3; **1** (R_1 = Cl), R = C_6H_5, R_2 = C_2H_5, R_3 = H, 19359-27-4; **1b**, 19359-28-5; **1c**, 19359-29-6; **2c**, 19359-30-9; 2(1H)-quinolone **2** (R, R_1, R_2, R_3), CH_3, Cl, H, 6-Cl, 19359-31-0; **2**, CH_2Br, Cl, H, 6-Cl, 19359-32-1; **2**

CH_2Br, CH_3, H, 6-Cl, 19359-33-2; **2**, C_6H_5, Cl, H, 6-Cl, 17259-82-4; **2**, C_6H_5, Cl, H, 6-CH_3, 19398-22-2; **2**, C_6H_5, Cl, C_2H_5H, 19359-35-4; **2**, C_6H_5, H, C_2H_5, 6-Cl, 19359-36-5; **3c**, 19359-37-6; **3d**, 19359-38-7; **3e**, 19375-64-5; **3f**, 19359-39-8; **3g**, 19359-40-1; **3h**, 19359-41-2; **3i**, 19359-42-3; **3j**, 19359-43-4; **3k**, 19359-44-5; **4b**, 19359-45-6; **4c**, 19359-46-7; **4d**, 19359-47-8; **4d** O-acetate, 19359-48-9; **4d** O-benzoate, 19359-49-0; **5**, 19359-50-3; **6**, 19359-51-4; **7**, 19359-52-5; **8a**, 19359-53-6; **8b**, 19359-54-7.

Synthesis and Cyclizations of Semicarbazidomethylenemalonates and Related Compounds

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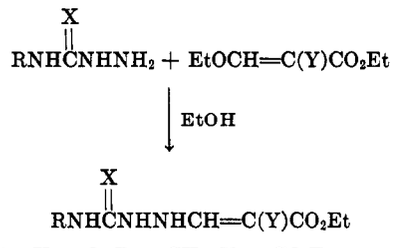
Reaction of semicarbazides and thiosemicarbazides with diethyl ethoxymethylenemalonate produced **1a–c** and **2a–c** in high yields. Use of ethyl 2-cyano-3-ethoxyacrylate led to **3a–c** and **4a–c**. Reaction of semicarbazides with ethoxymethylenemalononitrile (EMMN) produced **5a** and **b** and **6a** and **b**. Thiosemicarbazides and EMMN produced **7a** and **b**. Attempts to cyclize **1a** and **b** in hot ethanol were unsuccessful. Cyclization of **2a** and **2c** in hot ethanol gave 2-(ethylamino)- and 2-(anilino)-1,3,4-thiadiazole, respectively. Cyclization of **3a** gave **8a**, and **3b** gave **8b**, which readily lost the 1-phenylcarbamoyl group through solvolysis. Compound **4a** gave **9** upon cyclization, and **4c** gave ethyl 5-amino-4-pyrazolecarboxylate.

Hydrazinomethylenemalonates[1] and 3-hydrazino- and 3-(acylhydrazino)-2-cyanoacrylates[2,3] have been reported, and their cyclizations to pyrazole derivatives have been studied.[1–3] Hydrazines react with ethoxymethylenemalononitrile to produce pyrazoles *via* intermediate hydrazinomethylenemalononitriles which generally were not isolable.[4] Diethyl semicarbazidomethylenemalonate and diethyl thiosemicarbazidomethylenemalonate have been reported.[5] The reaction of semicarbazide with ethoxymethylenemalononitrile has been reported to give semicarbazidomethylenemalononitrile[6,7] under mild reaction conditions and 5-amino-4-cyano-1-pyrazolecarboxamide[8] under more vigorous reaction conditions.

We have studied the reactions of 4-substituted semicarbazides and 4-substituted 3-thiosemicarbazides with diethyl ethoxymethylenemalonate, ethyl 2-cyano-3-ethoxyacrylate, and ethoxymethylenemalononitrile. Reactions of semicarbazides and thiosemicarbazides with diethyl ethoxymethylenemalonate in ethanol at 20–25° gave semicarbazido- and thiosemicarbazidomethylenemalonates **1a–c** and **2a–c**, and use of ethyl 2-cyano-3-ethoxyacrylate in this condensation reaction gave **3a–c** and **4a–c** (Scheme I, Table I).

The reaction of semicarbazide with ethoxymethylenemalononitrile (EMMN) was reinvestigated; that semicarbazidomethylenemalononitrile[6,7] (**5a**) is obtained under mild reaction conditions was verified through

SCHEME I



1a, X = O; R = CH_3; Y = CO_2Et
b, X = O; R = C_6H_5; Y = CO_2Et
c, X = O; R = 3,4-$Cl_2C_6H_3$; Y = CO_2Et
2a, X = S; R = Et; Y = CO_2Et
b, X = S; R = allyl; Y = CO_2Et
c, X = S; R = C_6H_5; Y = CO_2Et
3a, X = O; R = CH_3; Y = CN
b, X = O; R = C_6H_5; Y = CN
c, X = O; R = 3,4-$Cl_2C_6H_3$; Y = CN
4a, X = S; R = Et; Y = CN
b, X = S; R = allyl; Y = CN
c, X = S; R = C_6H_5; Y = CN

nmr analysis of the product.[9] Reaction of 4-methylsemicarbazide with ethoxymethylenemalononitrile (EMMN) in ethanol at 23° led to (4-methylsemicarbazido)methylenemalononitrile[9] (**5b**) in 52% yield

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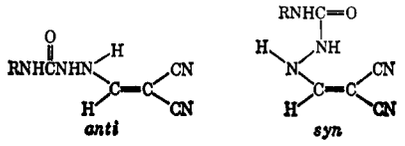
(9) The nmr spectra of **5a** and **5b** reveal hindered rotation about the vinyl carbon–nitrogen bond, with unequal populations of the *anti* and *syn* conformers; the vinyl proton and the adjacent NH proton each appear as two singlets of unequal intensity. Similarly, *anti–syn* isomerism has been observed with N-alkylaminomethylenemalononitriles (R. K. Howe, unpublished work),



and hindered rotation about the vinyl carbon–nitrogen bond of N,N-dimethylaminomethylenemalononitrile has been reported by A. Mannschreck and U. Koelle [*Tetrahedron Lett.*, 863 (1967)].