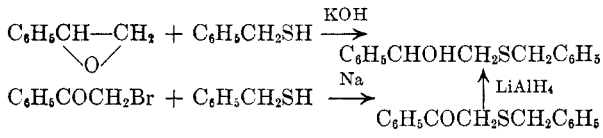
captides react with aliphatic oxides in the same fashion.[2]

In keeping with prediction, we observed that potassium benzyl mercaptide opened the oxide ring to form 1-phenyl-2-benzylmercaptoethanol in good yield. The product was identical with an authentic sample prepared from 1-phenyl-2-benzylmercaptoethanone by reduction with lithium aluminum hydride.



EXPERIMENTAL

Reaction of styrene oxide with benzyl mercaptan. A suspension of 11.2 g. (0.2 mole) of powdered potassium hydroxide in 75 ml. of dioxane was treated with 24.8 g. (0.2 mole) of benzyl mercaptan, and the mixture was stirred for 30 min. Then 24.0 g. (0.2 mole) of styrene oxide (Dow Chemical Co.) was added dropwise during 30 min. to the stirred suspension. The mixture was heated on the steam-bath during the addition, following which it was stirred for an additional 2 hours at room temperature.

Addition of water to the dark suspension caused the separation of two layers. The aqueous layer was extracted with ether, and the combined organic extracts were washed successively with dilute sulfuric acid, water, and a saturated sodium chloride solution, and then were dried with potassium carbonate. The product was purified by distillation, giving 37.6 g., 77%, b.p. 172–175° (1.5 mm.). An additional 2.3 g., b.p. 175–178° (1.5 mm.), distilled subsequently.

The main fraction solidified on chilling. When crystallized from ether-petroleum ether, there was obtained 20.6 g., m.p. 40–46°, and a second crop, 7.3 g., m.p. 42–47°. When recrystallized, the m.p. was 47–48°. The various mother liquors were combined, redistilled, and the main fraction was recrystallized. The total yield of pure material, m.p. 47–48°, was 23.4 g., 48%.

Another experiment using 0.4 g.-atom of potassium metal, 0.4 mole of benzyl mercaptan, and 0.1 mole of styrene oxide in 300 ml. of dioxane gave 56% of pure material when processed in the same way.

Synthesis of 1-phenyl-2-benzylmercaptoethanol. 1-Phenyl-2-benzylmercaptoethanone was prepared in 70% yield by the reaction of sodium benzylmercaptide with phenacyl bromide in alcohol by the procedure of Wahl[3]; m.p. 86–87°, reported,[3] 89°. Its dinitrophenylhydrazone was prepared by Brady's method[4]; m.p. 168.9–169.7° (acetic acid).

Anal. Calc'd for $C_{21}H_{18}N_4O_4S$: C, 59.70; H, 4.25. Found: C, 60.03; H, 4.33.

The ketone was reduced to the carbinol in 75% yield by refluxing it in ether with a slight excess of lithium aluminum hydride. The product was recrystallized from ether-petroleum ether, m.p. 46–47°. A mixture of this material with that prepared above melted at 46–47°, and their infrared spectra were identical.

Anal. Calc'd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 74.00; H, 6.40.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN

(2) Schuetz, *J. Am. Chem. Soc.*, **73**, 1881 (1951); Gilman and Fullhart, *J. Am. Chem. Soc.*, **71**, 1478 (1949); Culvenor, Davies, and Heath, *J. Chem. Soc.*, 278 (1949).

(3) Wahl, *Ber.*, **55**, 1454 (1922).

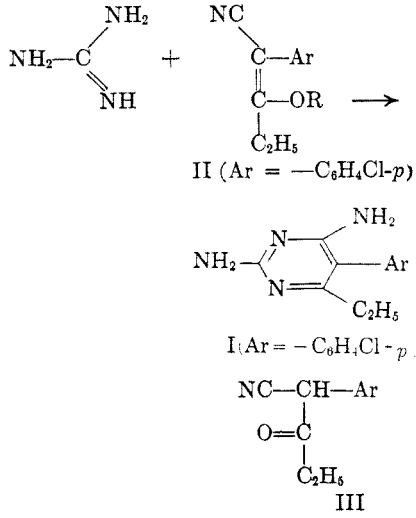
(4) Brady, *J. Chem. Soc.*, 756 (1931).

On the *O*-Methylation of α-Propionyl-*p*-chlorophenylacetonitrile

RICHARD BALTZLY AND PETER B. RUSSELL

Received April 20, 1956

The important antimalarial 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (pyrimethamine; Daraprim; I)[1] is prepared by the cyclization-condensation of guanidine with a β-alkyloxy-α-*p*-chlorophenyl-β-ethylacrylonitrile (II).[2] The compound II is the enol ether of the ketonitrile III. These enol ethers were originally prepared by treatment of the ketonitriles with diazomethane[2]



II (Ar = —C_6H_4Cl-*p*)

I (Ar = —C_6H_4Cl-*p*)

III

(giving II; R = Me); subsequently the reaction with ortho esters was employed[3] while more recently the Walker method, an acid catalyzed etherification, has been utilized.[4] This last method may be operated commercially although, at times, difficulties have been encountered.

The *O*-alkylation of the ketonitriles III with alkyl iodides and sulfates in aqueous or alcoholic potassium hydroxide solution[2,3] or in acetone solution in the presence of sodium carbonate[4a] met with indifferent success. Matti and Reynaud,[5] however, reported that under mild conditions cyandesoxybenzoin (IV) was converted by treatment with methyl sulfate and alkali into good yields of a mixture of the geometrically isomeric enol ethers Va and Vb. The findings of the French authors sug-

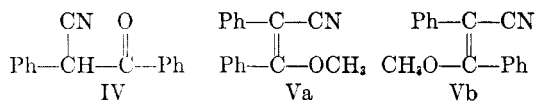
(1) Daraprim is the Burroughs Wellcome and Company (U.S.A.), Inc. trade name for pyrimethamine.

(2) Russell and Hitchings, *J. Am. Chem. Soc.*, **73**, 3763 (1951).

(3) Russell and Whittaker, *J. Am. Chem. Soc.*, **74**, 1310 (1952).

(4) (a) Chase, Thurston, and Walker, *J. Chem. Soc.*, 3439 (1951); (b) Chase and Walker, *J. Chem. Soc.*, 3518 (1953).

(5) Matti and Reynaud, *Compt. rend.*, **235**, 1231 (1952); Matti and Reynaud, *Bull. soc. chim. France*, **21**, 410 (1954).



IV Va Vb

gest that the cause of the failure of the earlier investigations[2,3] was due to the cleavage of the ketonitrile and that conditions for the conversion of III to II (R = CH_3) on a commercial scale might be found through the use of methyl sulfate. The present communication reports an examination of this reaction which has been developed into a commercially feasible method for the preparation of Daraprim.

The general working hypothesis in this study was that a displacement by the anion (synion) of the ketonitrile on the alkylating reagent ought to result in considerable amounts of the enol ether.[6] Since the pK_a of the ketonitrile was found to be 6.3[7c] it was evident that high alkalinities should be unnecessary. Early experiments using half neutralized ketonitrile in methanol were rather disappointing; there seemed to be no relationship between the consumption of alkali and the formation of the enol ether.[8] The low yields were not due to cleavage of the ketonitrile since this substance was recovered in good yield after standing in methanol at *p*H 8 (*i.e.*, 98% neutralized by alkali) for 18 hours. It was found that the difficulty arose from the solvolysis of the methyl sulfate by the alcohol which was unexpectedly rapid.[9] In methanol, at room temperature, methyl sulfate was found to have undergone solvolysis to the extent of about 67% in 16 hours. In 2-propanol about 20% of a sample of methyl sulfate had reacted in 1 hour. In aqueous dioxane (90% dioxane) on the other hand, hydrolysis occurred to only about 1–2% per hour.

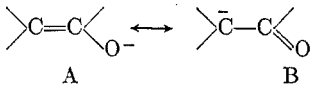
Initial experiments using aqueous dioxane showed that methylation with dimethyl sulfate did result in satisfactory yields of the enol ether. While there always remained a small alkali soluble residue, presumably unreacted ketonitrile, no evidence of appreciable C-alkylation was obtained. Failure to obtain quantitative yields was probably due to cleavage; this was not sensitive to temperature changes, however, for the yields remained constant up to steam bath temperature which permitted completion of the process in about 1 hour.

The gradual addition of alkali being inconvenient and a *p*H of 6.5–7 being sufficiently high, sodium bicarbonate was used as the base. The resultant system was not homogeneous and vigorous stirring was essential. The liquid phase showed an apparent *p*H of 6–6.5, and if an excess of bicarbonate was present, this *p*H remained essentially constant until the end of the reaction. When the reaction time was extended beyond that necessary for complete alkylation the mixture became gradually acid, presumably due to the hydrolysis of the reaction product of the methyl sulfate. Since this hydrolysis is acid-catalyzed it proceeds slowly so long as any bicarbonate remains, but, on consumption of the last traces of base, acidity develops rapidly. Since enol ethers are generally sensitive to acid hydrolysis, the acidity of the solution has a deleterious effect on the yields of Daraprim obtained.

Best results were obtained (yields of 60% estimated as Daraprim) using 4 equivalents of bicarbonate and 3 of methyl sulfate. When these proportions were reduced to 3:2 the yields of pyrimidine were about 50%. In small orienting runs (0.05 mole of ketonitrile) no condenser was used. In larger batches (0.25 mole or more) a reflux condenser was found to be necessary. Although the temperature of the reaction mixture never reaches the boiling point the escaping carbon dioxide carries off a considerable amount of solvent, presumably altering the composition of the portion that remains and so causing a drop in yield.

The solvent medium, 90% dioxane–10% water, may not be optimal but cannot be far from it. In the absence of water the reaction does not proceed at a significant rate. Successive runs with 2, 5, 6, and 7% of water approached those with 10%, the last three being only slightly inferior. Calcium car-

(6) This hypothesis can be rationalized on the following grounds. Where the tautomeric picture is not complicated by chelation it would seem that the structural influences that cause extensive enolization ought to produce a synion resembling the canonical structure A more than B. This argument could apply generally to systems involving non-



A B

chelate enols. It has been demonstrated that ketonitriles such as III or IV are extensively enolized and that the enols so formed are non-chelate.[7]

Some experimental evidence consistent with this principle is to be found in the several reports that ketonitriles give more *O*-alkylation than the corresponding β-ketoesters and also that 2-cyanocyclopentanone gives the *O*-alkyl derivative; von Auwers, *Ber.*, **61**, 412 (1928), Wiegand, *Dissertation, Marburg* (1927); Russell, *Chemistry & Industry*, 326 (1956).

A different view of the alkylation process is given by Brändström, *Arkiv. för Kemi*, **6**, 155 (1955).

(7) (a) Arndt, Löwe, and Ginkök, *Istanbul univ., Fen. Fac. Mecmuasi*, **A 11**, 154 (1946); (b) Russell, *J. Am. Chem. Soc.*, **74**, 2654 (1952); (c) Russell and Mentha, *J. Am. Chem. Soc.*, **77**, 4245 (1955).

(8) While many of the enol ethers II are crystalline, *e.g.*, II [Ar = —$C_6H_3Cl_2$(3,4), R = CH_3],[3] the Daraprim intermediate is not. Yields of enol ether in the above runs were estimated by reactions with guanidine to give the crystalline antimalarial. Condensations carried out with the crystalline ethers lead to the belief that this reaction is almost quantitative. It is possible that the oily ethers consist of a mixture of geometrical isomers and that one or the other of these might react poorly with guanidine. While this cannot be excluded entirely, we consider it improbable since guanidine adds satisfactorily to β,β-diethyl-α-arylacrylonitriles to give the corresponding 2,4-diaminodihydropyrimidines, Hitchings, Russell and Whittaker, *J. Chem. Soc.*, 1019 (1956).

(9) There appear to be no exhaustive studies on the rate of solvolysis of alkyl sulfates; *cf.* Kremann, *Monatsh.*, **27**, 1265 (1906); **28**, 13 (1907).

bonate although giving a satisfactory *p*H gave no product. Ethyl sulfate in place of methyl sulfate gave a 50% yield of pyrimethamine.

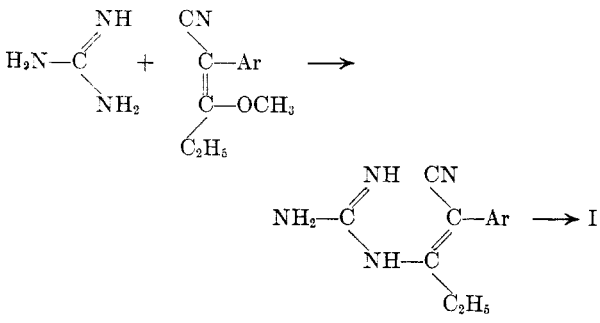
EXPERIMENTAL

In a 3-l. 3-necked flask fitted with a reflux condenser and a crescent-type stirrer was placed 210.5 g. of crude α-propionyl *p*-chlorophenylacetonitrile (calc'd as 1 mole but actually 85–90% material). To this was added 300 cc. ≈ 3 equivalents of methyl sulfate (commercial material but free of acid), 327.5 g. of sodium bicarbonate (3.9 equivalents), 720 cc. of dioxane, and 80 cc. of water. The flask was heated on a steam-bath and stirred vigorously. The reaction-temperature was 82.5° 22 minutes after the start and rose gradually to 87° an hour and a half later. The reaction was allowed to go 45 minutes further (probably unnecessary). The reaction mixture then was diluted with 800 cc. of benzene and 800 cc. of water and was cooled. The benzene layer was washed with water until approximately neutral. The aqueous layer and first wash neutralized 38 cc. of conc'd hydrochloric acid and therefore contained *ca.* 0.45 mole of bicarbonate—about half of the calculated excess. The benzene layer then was extracted with *N* alkali, washed with water, and evaporated to dryness *in vacuo*.

To the above oil was added a filtered solution of 1.1 moles of guanidine (from guanidine hydrochloride and sodium ethoxide) in 600 cc. of abs. ethanol. The solution was refluxed for four hours[10] and allowed to cool. The solid product weighed 134 g. and was pyrimethamine of good quality.

WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

(10) In the above and all of the other preparations of pyrimethamine it was observed that 10–20 minutes after the start of the reaction the flask became filled with a crystalline mush. On continued refluxing this material redissolved and was replaced by a much more compact solid which was the pyrimethamine. It is tempting to speculate as to the first solid being uncyclized addition product the probable course of the reaction being:[3]

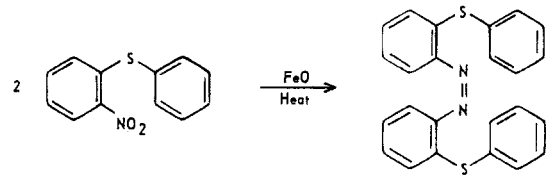


Reactions of 2-Nitrodiphenyl Sulfide and Related Sulfones in Attempted Ring Closure

DONALD L. VIVIAN AND HENRY C. WATERMAN

Received April 20, 1956

The synthesis of phenothiazine was attempted by subjecting 2-nitrodiphenyl sulfide to the action of ferrous oxide (from ferrous oxalate) at 275–285°. This method is analogous to that used by Waterman and Vivian[1] for the preparation of phenazine by ring closure of 2-nitrodiphenylamine through the nitro group. From the reaction there was obtained a compound melting at 188–189°, in the form of small, matted orange needles. While its analysis agreed with the theory for phenothiazine (m.p. 184–185°), a pronounced depression of the melting point of a mixture of the two showed it not to be the desired compound. Consideration of other structures having the same empirical formula suggested 2,2′-bis(phenylmercapto)azobenzene, and titration with $TiCl_3$ supported this view. Hence the reaction appears to have been:



When the 2-nitrodiphenyl sulfide was converted to the corresponding sulfone, and this substance was subjected to the same reaction conditions, the resulting product was not an azo compound, but was the known 2-aminodiphenyl sulfone, as shown by the analysis and melting point.

In like fashion, both 4-chloro-2-nitrodiphenyl sulfone and 5-chloro-2-nitrodiphenyl sulfone gave the corresponding amino compounds when subjected to high-temperature reduction by ferrous oxalate dihydrate.

EXPERIMENTAL

2,2′-bis(Phenylmercapto)azobenzene. A mixture of 0.6 g. of 2-nitrodiphenyl sulfide,[2] 0.8 g. of ferrous oxalate dihydrate, and 8 g. of granulated lead was heated in an oil-bath at 270–280° for 25 minutes. Vacuum sublimation from an oil-bath at 250°, pressure about 2 mm., gave 0.4 g. of an orange-red product melting at 182–184° to a dark red liquid, without decomposition. Recrystallized twice from absolute alcohol, the compound formed small, matted orange needles, m.p. 188–189°.[3]

Anal.[4] Calc'd for $C_{24}H_{18}N_2S_2$: C, 72.4; H, 4.55; N, 7.05; S, 16.0. Found: C, 72.4; H, 4.90; N, 7.19; S, 15.8.

This compound gave an immediate deep green color with concentrated sulfuric acid, while phenothiazine gave a dull red. A mixture melting point determination gave 157–179°, proving that the compound was not phenothiazine.

Evidence of its azo structure was given by its behavior on titration in aqueous alcohol by $TiCl_3$,[5] which was that of a typical azo compound, resulting in a colorless solution.

Anal. Calc'd for $C_{24}H_{18}N_2S_2$: $TiCl_3$ required for 31.2 mg. sample, 36.5 mg.; Found: 32 mg. (some small part of the compound was not in solution).

(1) Waterman and Vivian, *J. Org. Chem.*, **14**, 289 (1949).

(2) Tarbell, Todd, Paulson, Lindstrom, and Wystrach, *J. Am. Chem. Soc.*, **70**, 1384 (1948).

(3) All melting points are corrected.

(4) Analyses by the Microanalytical Laboratory of the National Institutes of Health, under the direction of Dr. W. C. Alford.

(5) Titration by $TiCl_3$ courtesy of Dr. Kenneth A. Freeman, Chief, Color Certification Branch, Food & Drug Administration.