Alkylation by Secondary Alcohols III: Fusion of Medicinal Sulfanilamides with Benzhydrol

R. E. MOSKALYK [x] and J. L. MALICKY

Abstract □ The fusion of certain sulfanilamides with benzhydrol in the presence of anhydrous zinc chloride affords several different products, depending primarily on the temperature at which the reaction is carried out. With sulfanilamide itself, three different products were isolated at 100, 160, and 180°. A sequence of steps is suggested to account for the three products, one of which involves an intramolecular rearrangement of a benzhydryl moiety. The fusion of benzhydrol with *p*-toluidine gives 2,6-dibenzhydrylaniline and not the *N,N*-dibenzhydryl derivative as previously reported.

Keyphrases □ Sulfanilamides—fusion with benzhydrol, effect of reaction temperature, isolation and identification of products □ Benzhydrol—fusion of medicinal sulfanilamides, alkylation by secondary alcohols, effect of temperature □ Alkylation—by secondary alcohols, fusion of medicinal sulfanilamides with benzhydrol, effect of reaction temperature

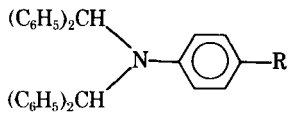
Sulfanilamides yield a number of interesting and useful substitution products when reacted with certain secondary alcohols under various reaction conditions. Initially, this reaction was studied employing xanthydrol as the alkylating agent (1). More recently, the reaction of sulfanilamides with benzhydrol in nitromethane, using perchloric acid as the catalyst, was reported (2). The products were normally the corresponding N^4-monobenzhydryl derivatives of type I and these proved to be stable crystalline compounds most suitable for the identification and differentiation of the antibacterial sulfanilamides.

The fusion of benzhydrol with a number of *para*-substituted anilines, in the presence of zinc chloride, gave the corresponding *N,N*-dibenzhydryl derivatives (II) (3, 4). Since this type of substitution had not been previously encountered in this laboratory under any reaction conditions, this investigation was initiated to prepare and study the products of the fusion reaction involving benzhydrol and the various sulfanilamides.

These compounds would be interesting not only from the standpoint of their potential use in the qualitative analysis of this class of drugs but also as model compounds for theoretical studies of both the structure–activity relationships and the mode of action of the medicinal sulfanilamides.

EXPERIMENTAL[1]

2,6-Dibenzhydryl-4-methylaniline (III)—Compound III was



II

R = $(C_6H_5)_2CH$ (3), CH_3, $CH(CH_3)_2$, Cl, Br, NO_2, $COOCH_3$, $COOCH_2CH_3$, OCH_3, and OCH_2CH_3 (4)

obtained by following the method reported by Giraud (4) for the preparation of *N,N*-dibenzhydryl-4-methylaniline (II, R = CH_3). To 2 g (0.019 mole) of *p*-toluidine and 3.5 g (0.038 mole) of benzhydrol was added 1 g of zinc chloride. The reaction mixture was heated in an open tube in a glycerin bath for 2 hr at approximately 150°.

After cooling, the solid residue was stirred with ethanol, resulting in the immediate formation of fine crystals which melted at 188° after several crystallizations from ethanol [lit. (4) mp 188° for the product of this reaction]; IR (mineral oil): 3390 and 3322 (NH_2) cm^{-1}; NMR ($CDCl_3$): τ 2.82 (s, 20H, C_6H_5), 3.55 (s, 2H, aromatic), 4.53 (s, 2H, methine), 6.74 (s, 2H, NH_2, D_2O exchangeable), and 8.03 (s, 3H, CH_3).

Anal.—Calc. for $C_{33}H_{29}N$: C, 90.16; H, 6.65; N, 3.19. Found: C, 90.14; H, 6.54; N, 3.42.

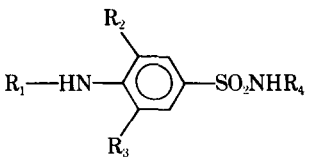
N^1-(2-Pyridyl)-N^4,3-dibenzhydrylsulfanilamide (IV)—Compound IV was obtained by fusing 1.0 g (0.004 mole) of sulfapyridine with 1.47 g (0.008 mole) of benzhydrol in the presence of 1.1 g (0.008 mole) of zinc chloride at 150° for 10 min. The same product was also obtained from a similar reaction mixture fused for 45 min at 185°. Stirring with ethanol afforded a white product which, after three crystallizations from ethanol, melted at 232.5–234.5°; IR (mineral oil): 3390 (NH) and 1147 (SO_2) cm^{-1}.

Anal.—Calc. for $C_{37}H_{31}N_3O_2S$: C, 76.39; H, 5.37; N, 7.22. Found: C,,76.26; H, 5.43; N, 7.07.

N^1-(2-Pyrimidyl)-N^4,3-dibenzhydrylsulfanilamide (V)—Compound V was prepared by fusing 2.2 g (0.005 mole) of benzhydrol and 1.8 g (0.01 mole) of sulfadiazine in the presence of 1.36 g (0.01 mole) of zinc chloride at 150° for 5 min. Treatment of the cooled reaction mixture with ethanol yielded the title compound which, when recrystallized twice from an acetone–water mixture, melted at 249–250°; IR (mineral oil): 3367 (NH) and 1163 (SO_2) cm^{-1}.

Anal.—Calc. for $C_{36}H_{30}N_4O_2S$: C, 74.20; H, 5.19; N, 9.62. Found: C, 74.24; H, 5.22; N, 9.48.

3,5-Dibenzhydrylsulfanilamide (VI)—Fusion of 2.2 g (0.012



compound	R_1	R_2	R_3	R_4
I	$(C_6H_5)_2CH$	H	H	H
IV	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	H	2-pyridyl
V	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	H	2-pyrimidyl
VI	H	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	H
VII	H	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	9-xanthenyl
VIII	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	H	$(C_6H_5)_2CH$
IX	H	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$	$(C_6H_5)_2CH$
X	H	H	H	H
XI	$(C_6H_5)_2CH$	H	H	$(C_6H_5)_2CH$

[1] Melting points were determined using a Thomas-Hoover capillary melting-point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer IR spectrophotometer, model 21, as Nujol mulls. NMR spectra were taken on a Varian Associates model A-60 spectrometer. Elemental analyses were performed by Messrs. Weiler and Strauss, Oxford, England, and by the Microanalysis Laboratory, Department of Chemistry, University of Alberta. Benzhydrol was obtained as the commercial product from Eastman Kodak Co., Rochester, N.Y., and used without further purification. The sulfanilamides were obtained commercially or were gifts from the manufacturers.

mole) of benzhydrol and 1.0 g (0.006 mole) of sulfanilamide in the presence of 1.6 g (0.012 mole) of zinc chloride for 30 min at 180° yielded a pasty material. On cooling and stirring with ethanol, the title compound was isolated, mp 296–297° (ethanol); IR (mineral oil): 3378, 3300, and 3205 (NH_2 and SO_2NH_2) cm^{-1}.

Anal.—Calc. for $C_{32}H_{28}N_2O_2S$: C, 76.16; H, 5.59; N, 5.55. Found: C, 76.25; H, 5.81; N, 5.35.

N′,3,5-Tribenzhydrylsulfanilamide (IX)—Fusion of 3.0 g (0.016 mole) of benzhydrol and 1.0 g (0.006 mole) of sulfanilamide in the presence of 2.2 g (0.016 mole) of zinc chloride at 160° for 3 min, followed by stirring in ethanol, yielded a white product. After several recrystallizations from ethanol, the compound melted at 296°. A mixed melting point with VI showed no depression.

The remainder of the solution was concentrated and the gummy residue was extracted with chloroform. Upon evaporation of the chloroform, a gummy material was again isolated. However, stirring the gum in ethanol yielded a white precipitate which, after several crystallizations from ethanol, melted at 193–194.5°; IR (mineral oil): 3390 and 3300 (NH_2) cm^{-1}.

Anal.—Calc. for $C_{45}H_{38}N_2O_2S$: C, 80.56; H, 5.71; N, 4.18. Found: C, 80.69; H, 5.78; N, 4.42.

N′-Xanthenyl-3,5-dibenzhydrylsulfanilamide (VII)—Compound VII was prepared by reacting VI with xanthydrol following the procedure of Moskalyk and Chatten (1); mp 207–208° (acetone–water); IR (mineral oil): 3356, 3249, and 3289 (NH_2 and SO_2NH) cm^{-1}.

Anal.—Calc. for $C_{45}H_{36}N_2O_2S$: C, 78.92; H, 5.30; N, 4.09. Found: C, 78.38; H, 5.31; N, 4.40.

The compound could not be purified further.

RESULTS AND DISCUSSION

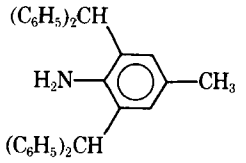
The physical properties of the first few compounds isolated from the fusion reaction with several sulfanilamides did not appear to correspond to the type of structure illustrated by II. Accordingly, the reaction of one of the compounds reported by Giraud (4), *p*-toluidine, was reexamined. Upon duplicating the procedure, a compound with an identical melting point (188°) to that reported was recovered. Elemental analysis verified that the compound was a disubstituted derivative. However, examination of the NMR and IR spectra revealed that the product was 2,6-dibenzhydryl-4-methylaniline (III).

The NMR spectrum consisted of five very well-resolved singlets. A 20-proton singlet at τ 2.82 accounted for the aromatic protons on the two benzhydryl groups. Three two-proton singlets at τ 3.55, 4.53, and 6.74 accounted for the aromatic, methine, and amino protons, respectively. The latter protons exchanged on deuteration. The last singlet, representing three protons, could be assigned to the methyl group (τ 8.03). In the IR, the spectrum still exhibited two peaks in the amino-stretching region, although these were depressed in intensity when compared to the parent amine.

In view of these results, the structure assigned to this compound by Giraud (4) (II, R = CH_3) is incorrect. Furthermore, this same structural assignment made to the eight other *para*-substituted aniline derivatives represented in II now appear to be in doubt also.

Sulfacetamide, when fused with benzhydrol at 150° for 2 hr, gave a product which did not exhibit any carbonyl or sulfonyl absorption in the IR region. It was shown to be 2,6-dibenzhydrylaniline[2], a compound that had been isolated previously from a reaction of *p*-aminobenzoic acid with benzhydrol (2). Fusion of the latter two compounds also gave 2,6-dibenzhydrylaniline.

Under similar reaction conditions, sulfapyridine failed to give a recoverable product. However, when the reaction was interrupted after 10 min at 150°, a white crystalline material was recovered which proved to be the dibenzhydryl derivative IV. The IR spectrum showed but a single band in the amino-stretching region characteristic of N^4-monosubstitution. The sulfonamide hydrogen was not substituted, as evidenced by the titratability of the compound as an acid[3]. The SO_2 symmetric stretching frequency at



III

1147 cm^{-1} suggested that the compound existed in the amido tautomeric form[4], as illustrated in IV. Treatment of N^4-monobenzhydrylsulfapyridine, prepared earlier (2), with benzhydrol under these fusion conditions gave IV, further supporting this structural assignment.

Sulfadiazine also yielded a disubstituted derivative when fused with benzhydrol in the presence of zinc chloride for 5 min. This product was likewise shown to be substituted on the amino nitrogen and in the position *ortho* to the nitrogen (V). These compounds (IV and V) represent yet another type of substitution pattern possible under fusion conditions and thus cast further doubt on the validity of Giraud's structural assignments.

Fusing sulfabenz with benzhydrol for 2 min afforded a monosubstituted product in very low yield. The compound was shown to be the N^4-monobenzhydryl derivative[5] reported previously. No disubstituted derivatives could be isolated from any of the fusion reactions carried out for longer periods.

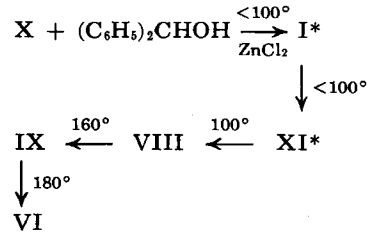
The preceding observations suggest that the first step in the alkylation reactions under fusion conditions is the substitution of a hydrogen on the N^4-nitrogen atom. This conclusion was borne out in the more detailed studies of the fusion reaction with sulfanilamide itself.

Sulfanilamide, when fused with a 2 molar ratio of benzhydrol at 180° for 30 min, afforded the dibenzhydryl derivative VI. Reaction of VI with xanthydrol gave VII. Employing a 3:1 molar ratio of benzhydrol to sulfanilamide, under identical reaction conditions, again gave VI, as did the reaction with a 5:1 molar ratio. The failure of these reactions with large excesses of benzhydrol to give derivatives alkylated also at the N'-position was puzzling in view of the ease with which this site can be alkylated with either benzhydrol (2) or xanthydrol (1) in solution.

Since alkylation at the N'-position with xanthydrol proceeds readily at room temperature and that with benzhydrol proceeds readily at about 70°, it seemed probable that N'-benzhydryl derivatives were being formed in the reaction but that they were subsequently cleaved at these higher fusion temperatures (150–180°). In support of this postulate, when a 3 molar ratio of benzhydrol was fused with sulfanilamide at 100° for 5 min, VIII[6] was isolated in high yield. To exemplify further the influence of the temperature, fusion of benzhydrol with sulfanilamide (3:1 molar ratio) at 160° afforded two compounds: VI and IX. Reaction of VI with benzhydrol in nitromethane and perchloric acid catalyst gave IX; with xanthydrol, it gave VII.

The preceding results suggest the sequence of steps for the reaction of benzhydrol with sulfanilamide at different fusion temperatures illustrated by Scheme I.

Although I and XI were not isolated under fusion conditions, I had been recovered previously from the corresponding reaction in



*Scheme I—*Not isolated under fusion conditions*

[2] Isolated from the reaction mixture after stirring with ethanol, mp 174–175.5° (acetone–water) [lit. (2) mp 174–175.5°]; IR (mineral oil): 3425 and 3356 (NH_2) cm^{-1}.

[3] Titrated in chloroform with 0.1 *N* KOH in methanol, using phenolphthalein as the indicator.

[4] The SO_2 symmetric stretching frequencies in the 1160–1145 and 1145–1125 cm^{-1} ranges have been assigned to the amido and imido forms, respectively (1, 5).

[5] Isolated by extraction of the gummy residue with chloroform, mp 215–216° (ethanol) [lit. (2) mp 216–218°].

[6] With a melting point of 206–208° (dioxane–water) [lit. (2) mp 206–208°].

solution (2) and the xanthenyl analog of XI had been reported (1). The formation of VIII from an equimolar reaction suggests that the monosubstituted derivative I is more reactive than the parent sulfanilamide X to further alkylation and that the resulting product XI is even more susceptible to further alkylation.

The conversion of VIII to IX at 160° involves the rearrangement of a benzhydryl moiety from the N^4-position to the second *ortho*-position on the phenyl ring. Some evidence was obtained to imply that this migration is an intramolecular one and could either occur by a concerted process or through an ion-pair intermediate. When VIII was heated in the presence of zinc chloride and pure sulfanilamide (X), the only product that could be isolated was IX, and there was no indication of any cross-products of an intermolecular process being formed. When this reaction was repeated using naphthalene rather than sulfanilamide, once again IX was the only product isolated. Fusion of I with sulfanilamide in the presence of zinc chloride somewhat surprisingly gave VI. Since no free benzhydrol was present in the reaction mixture, the second benzhydryl radical must have come from another molecule of I. This result tends to support an intramolecular rearrangement *via* an ion-pair mechanism.

When VIII was heated at 210° with an equal weight of sulfanilamide (X) in the absence of zinc chloride, only starting material was recovered. Therefore, these benzhydryl rearrangements are not simply thermodynamic, and the zinc chloride obviously functions as a Lewis acid in a manner analogous to that found in the benzidine rearrangement.

Rearrangements involving benzhydryl groups have been reported, but the mechanistic aspects have not been studied in detail. The rearrangement of the benzhydryl ether of *o*-cresol, in the presence of zinc chloride, to give the corresponding *p*-benzhydryl-*o*-methylphenol was reported (6), and the rearrangement of *N*-benzhydrylsalicylamide to the corresponding *para*-substituted phenol was observed (7). *N*-Benzhydryl-*o*-toluidine was found to yield two products, the *p*-benzhydryl- and the *o,p*-dibenzhydrylanilines, when heated in a hydrochloric–acetic acid medium (8). When the reaction was carried out in the presence of *o*-cresol, the cross-product, *p*-benzhydryl-*o*-methylphenol, was also recovered; accordingly, it was concluded that the rearrangement occurred through an intermolecular process. The apparent intramolecular rearrangement of the benzhydryl group observed in this study does not appear to have a precedent.

Attempted fusion reactions with sulfamerazine, sulfamethazine, sulfachlorpyridazine, sulfamethoxypyridazine, sulfaphenazole, sulfaquinoxaline, sulfamethoxazole, sulfadimethoxine, sulfaproxyline, sulfisoxazole, sulfamethizole, sulfathiazole, sulfaethidole, and sulfaguanidine afforded gums which could not be crystallized. Numerous attempts employing different reaction temperatures, different reaction times, and varying amounts of catalyst with each sulfanilamide invariably gave unresolvable gums. The only exceptions were sulfaquinoxaline[7] and sulfamethizole[8], both of which afforded the corresponding N^4-monobenzhydryl derivatives at lower fusion temperatures for shorter periods. Therefore, contrary to the report by Giraud (4), this reaction, under the conditions used in this study, did not yield *N,N*-dibenzhydryl derivatives with *para*-substituted anilines nor any other readily recoverable products with the majority of the sulfanilamides studied.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 3, 1974, from the *Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada, T6G 2H7*

Accepted for publication September 13, 1974.

Supported by the National Research Council of Canada.

The authors thank the following pharmaceutical manufacturers for the generous gifts of sulfanilamides used in this study: Ayerst; McKenna and Harrison Ltd.; Ciba Co. Ltd.; Geigy Pharmaceuticals; Hoffmann–La Roche Ltd.; Horner, Frank W. Ltd.; Lederle Laboratories Ltd.; Merck Sharp and Dohme of Canada Ltd.; Parke-Davis and Co. Ltd.; Schering Corp. Ltd.; Smith Kline and French; and Winthrop Laboratories.

[x] To whom inquiries should be directed.

[7] Fusion at 130° for 10 min, mp 223–225° (acetone–water) [lit. (2) mp 224–225°].

[8] Fusion at 130° for 5 min and stirring of the residue with ethanol, mp 214–215.5° (chloroform–hexane) [lit. (2) mp 212–212.5°].