Alkylation by secondary alcohols. I. The reaction of xanthydrol with some N^1-monosubstituted sulfanilamides and related compounds

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Sulfanilamides were found to undergo alkylation with xanthydrol, yielding either mono- or di-xanthenyl derivatives. The site of substitution, common to all sulfanilamides having a free *p*-amino group, was shown to be the N^4-position in the sulfanilamide molecule. Three additional unique reactive sites were observed. Sulfanilamides carrying a thiazole, thiadiazole, or pyridazine substituent in the N^1-position were also alkylated on the annular nitrogen atom of the heterocyclic ring, the reaction having occurred from the imido tautomeric form. Sulfisoxazole (I*k*), on the other hand, reacted from the amido form to give the N^1,N^4-dixanthenyl derivative. Sulfadimethoxine (I*h*) was substituted at carbon, as well as at nitrogen, to yield N^4-xanthenyl-N^1-(2,6-dimethoxy-5-(9-xanthenyl)-4-pyrimidyl)sulfanilamide.

Sulfanilamides possessing pK_a values of about 5.5 were found to be sufficiently acidic to catalyze their own reaction with xanthydrol, and no external catalyst was necessary. The exceptional ease of formation of the xanthylium ion was postulated to be associated with the resulting stability of this carbonium ion by virtue of its acquired aromatic character.

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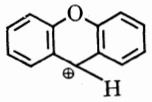
INTRODUCTION

Xanthydrol is an exceptionally reactive secondary alcohol. In comparative studies it has been shown to be more reactive than benzhydrol (1–4) and more reactive even than the tertiary alcohol triphenylcarbinol (3, 5). This exceptional reactivity has often been acknowledged but has never been explained satisfactorily. Reactions with xanthydrol involve the xanthylium ion (I),



I

which is apparently readily formed in glacial acetic acid. Nucleophilic attack by an electron pair from a molecule of relatively high electron density leads to the substitution product. Simple mixing of the reactants in glacial acetic acid at room temperature, or with slight heating, is usually sufficient to allow the reaction to proceed. The readily formed products are easily purified, and are therefore suitable for the characterization of the parent compounds. Examples of compounds which have been condensed with this carbinol include those with active methylene groups, those with active aromatic rings, ureas, semicarbazides, hydrazines, primary amides, imides, amines, sulfonamides, and mercaptans (6).

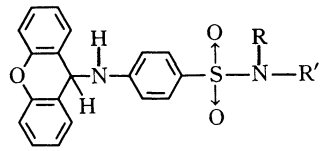
Primary benzenoid sulfonamides condense with the reagent to yield the corresponding *N*-xanthenylsulfonamides (7). The secondary sulfonamide *N*-ethyl-*p*-toluenesulfonamide failed to react, confirming earlier observations with secondary carboxyamides (8–10). Sulfanilamide, on the other hand, reacted with xanthydrol to give a disubstituted product postulated to be 3,N^1-dixanthenylsulfanilamide. In view of the above, N^1-monosubstituted sulfanilamides would be expected to yield 3-xanthenyl derivatives. Two such sulfanilamides have been condensed with xanthydrol, but the products were assigned N^4-xanthenyl structures (11).

The present study resolved this apparent difference in the site of substitution, and also revealed several additional interesting and unique substitution behaviors. Certain sulfanilamides were found to be sufficiently acidic to catalyze their own reaction with xanthydrol, further exemplifying the great reactivity of this carbinol. An explanation has been offered to account for the exceptional reactivity of xanthydrol.

RESULTS AND DISCUSSION

Condensation of the sulfanilamides with xanthydrol occurred readily, most of the

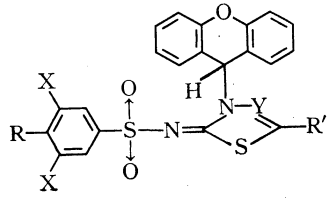
TABLE I

Summary of data for 

	Reactant	R	R′	Melting point (°C)*	Recrystallization solvent†	Formula	Calculated C	Calculated H	Calculated N	Calculated Equiv. wt.	Found C	Found H	Found N	Found Equiv. wt.
I*a*	Sulfanilamide	H	9-Xanthenyl	209–210‡	a–h	$C_{32}H_{24}N_2O_4S$	72.16	4.54	5.26	—	72.19	4.52	5.06	—
I*b*	Sulfacetamide	H	Acetyl	208–208.5	p–w	$C_{21}H_{18}N_2O_4S$	63.94	4.60	7.10	394.4	63.68	4.82	7.40	393.7
I*c*	Sulfaproxyline	H	*p*-Isopropoxybenzoyl	192–193	p–w	$C_{29}H_{26}N_2O_6S$	67.68	5.09	5.45	514.6	67.71	5.08	5.43	520.9
I*d*	Sulfanilanilide	H	Phenyl	185–186	a–h	$C_{25}H_{20}N_2O_3S$	70.07	4.71	6.54	428.5	69.65	4.78	6.56	432.5
I*e*	Sulfadiazine	H	2-Pyrimidyl	229–229.5§	p–w	$C_{23}H_{18}N_4O_3S$	64.17	4.21	13.02	430.5	64.44	4.26	12.75	437.8
I*f*	Sulfamerazine	H	4-Methyl-2-pyrimidyl	206–207	p–w	$C_{24}H_{20}N_4O_3S$	64.85	4.54	12.60	444.5	64.73	4.60	12.78	449.2
I*g*	Sulfamethazine	H	4,6-Dimethyl-2-pyrimidyl	173.5–174.5	a–h**	$C_{25}H_{22}N_4O_3S$	65.48	4.84	12.22	458.5	65.55	4.87	12.19	489.5
I*h*	Sulfadimethoxine	H	2,6-Dimethoxy-5-(9-xanthenyl)-4-pyrimidyl	199–200	c–h‡‡	$C_{38}H_{30}N_4O_6S$	68.04	4.51	8.35	670.7	64.62††	4.48	8.10	680.5
I*i*	N^1-Acetylsulfamethoxypyridazine	Acetyl	6-Methoxy-3-pyridazinyl	217.5–218.5	a–h**	$C_{26}H_{22}N_4O_5S$	62.14	4.41	11.15	—	61.46††	4.49	11.20	—
I*j*	Sulfamethoxazole	H	5-Methyl-3-isoxazolyl	205–205.5	a–h	$C_{23}H_{19}N_3O_4S$	63.73	4.42	9.69	433.5	64.00	4.63	9.60	437.7
I*k*	Sulfisoxazole	9-Xanthenyl	3,4-Dimethyl-5-isoxazolyl	178.5–179	a–h	$C_{27}H_{29}N_3O_6S$	70.79	4.66	6.69	627.7	70.88	4.45	6.68	—
I*l*	N^1-Acetylsulfisoxazole	Acetyl	3,4-Dimethyl-5-isoxazolyl	188–189	a–h¶	$C_{26}H_{23}N_3O_6S$	63.79	4.74	8.58	—	63.90	4.74	8.65	—
I*m*	Sulfaphenazole	H	1-Phenyl-5-pyrazolyl	228–228.5	a–h	$C_{28}H_{22}N_4O_3S$	68.00	4.48	11.33	494.6	68.19	4.76	11.35	521.8
I*n*	Metachloridine‖	H	5-Chloro-2-pyrimidyl	221.5–222	a–h	$C_{23}H_{17}ClN_4O_3S$	59.41	3.69	12.05	464.9	59.38	3.70	12.11	464.7

*All compounds melted with decomposition.
†a = acetone, h = hexane, p = pyridine, w = water, and c = chloroform. All recrystallizations were carried out at room temperature.
‡Literature (7) m.p. 208–209°.
§Literature (11) m.p. 246–247°.
‖9-Xanthenylamino moiety in the meta rather than the para position.
¶After several crystallizations from acetone–water.
**After several crystallizations from pyridine–water.
††Could not be purified further.
‡‡Recrystallization from ethyl acetate – *n*-hexane yielded the N^1-monoxanthenyl derivative, m.p. 176.5–177°.
Anal. Calcd. for $C_{25}H_{22}N_4O_5S$: C, 61.21; H, 4.52; N, 11.39. Found: C, 60.84; H, 4.52; N, 11.01.

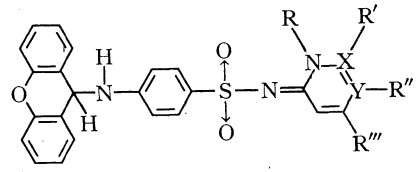
TABLE II

Summary of data for 

	Reactant	R	R′	X	Y	Melting point (°C)*	Recrystallization solvent†	Formula	Calculated C	Calculated H	Calculated N	Calculated Equiv. wt.	Found C	Found H	Found N	Found Equiv. wt.
II*a*	Sulfathiazole	9-Xanthenylamino	H	H	C	179–180	p–w‡	$C_{35}H_{26}N_3O_4S_2$	68.27	4.09	6.83	615.7	68.35	4.01	6.54	—
II*b*	Succinylsulfathiazole	Succinylamino	H	H	C	173.5–174.5	d–w	$C_{26}H_{21}N_3O_6S_2$	58.31	3.95	7.85	535.6	57.94	4.07	8.13	545.5
II*c*	Phthalylsulfathiazole	Phthalylamino	H	H	C	153–153.5	a	$C_{30}H_{21}N_3O_6S_2$	61.73	3.63	7.20	—	61.15	3.90	7.34	—
II*d*	*p*-Nitrosulfathiazole	Nitro	H	H	C	166–166.5	c–h	$C_{22}H_{15}N_3O_6S_2$	56.76	3.25	9.03	465.5	56.10‖	3.30	8.31‖	—
II*e*	Sulfamethizole	9-Xanthenylamino	Methyl	H	N	206.5–207	a–w‡	$C_{35}H_{26}N_4O_4S_2$	66.65	4.15	8.88	630.7	66.62	4.16	8.90	—
II*f*	Sulfaethylthiadiazole	9-Xanthenylamino	Ethyl	H	N	210.5–211.5	p–w‡	$C_{36}H_{28}N_4O_4S_2$	67.06	4.38	8.69	644.7	66.96	4.44	8.73	—
II*g*	3,5-Dibromosulfaethylthiadiazole§	Amino	Ethyl	Br	N	200–201	e	$C_{23}H_{18}Br_2N_4O_3S_2$	44.38	2.92	9.00	622.4	44.69	3.18	9.08	—
II*h*	Isobuzole	Methoxy	Isobutyl	H	N	170–170.5	e	$C_{26}H_{25}N_3O_4S_2$	61.52	4.96	8.28	507.6	61.37	4.95	8.17	—

*All compounds, with the exception of the last two, melted with decomposition.
†p = pyridine, w = water, d = dioxane, a = acetone, c = chloroform, h = hexane, and e = ethanol.
‡Carried out at room temperature.
§Anal. Calcd.: Br, 25.68. Found: Br, 25.42.
‖Could not be purified further.

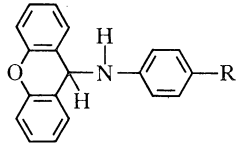
TABLE III

Summary of data for 

	Reactant	R	R′	R″	R‴	X	Y	Melting point (°C)*	Recrystallization solvent†	Formula	Calculated C	Calculated H	Calculated N	Calculated Equiv. wt.	Found C	Found H	Found N	Found Equiv. wt.
III*a*	Sulfapyridine	H	H	H	H	C	C	220–221‡	p–h	$C_{24}H_{19}N_3O_3S$	67.11	4.46	9.78	429.5	66.96	4.72	9.75	431.6
III*b*	Sulfisomidine	H	CH_3	—	CH_3	C	N	180–182	p–w	$C_{25}H_{22}N_4O_3S$	65.48	4.84	12.22	458.5	65.55	4.92	11.95	459.3
III*c*	Sulfachloro-pyridazine	9-Xanthenyl	—	Cl	H	N	C	184.5–185.5	p–w	$C_{36}H_{25}ClN_4O_4S$	67.02	3.91	8.68	645.1	66.90	4.20	8.82	—
III*d*	Sulfamethoxy-pyridazine	9-Xanthenyl	—	OCH_3	H	N	C	223–224	p–w	$C_{37}H_{28}N_4O_5S$	69.36	4.40	8.74	640.7	69.51	4.20	8.66	—

*All compounds melted with decomposition.
†p = pyridine, h = hexane, and w = water. All recrystallizations were carried out at room temperature.
‡Literature (11) m.p. 241–242°.

TABLE IV

Summary of data for 

	Reactant	R	Melting point (°C)*	Recrystallization solvent†	Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
IV*a*	Sulfaguanidine	$SO_2N{=}C(NH_2)_2$	225.5–226.5	p–h	$C_{20}H_{18}N_4O_3S$	60.90	4.60	14.20	60.87	4.62	14.35
IV*b*	Sulfaguanidine	$SO_2N{=}C(NH_2)NHX$‡	230.5–231.5	p–w	$C_{33}H_{26}N_4O_4S$	68.97	4.56	9.75	68.01§	4.64	9.66
IV*c*	*p*-Aminobenzoic acid	COOH	173.5–174	a–h	$C_{20}H_{15}NO_3$	75.69	4.77	4.41	75.80	5.88§	4.27
IV*d*	Ethyl-*p*-aminobenzoate	COOEt	200–201	a–w	$C_{22}H_{19}NO_3$	76.50	5.54	4.06	76.52	5.72	4.15

*All compounds melted with decomposition.
†a = acetone, h = hexane, p = pyridine, and w = water. All recrystallizations were carried out at room temperature.
‡X = 9-xanthenyl.
§Could not be purified further.

products separating from the reaction mixture in a matter of minutes. The resulting crude derivatives, although apparently stable when dry, decomposed upon attempted recrystallization from hot solvents. Accordingly, the recrystallizations were performed at room temperature with mixed solvent systems. Pyridine proved to be the most consistently effective primary solvent, but presented a problem with regard to its ultimate removal since, once again, heat could not be employed.

Of the 30 sulfanilamides and related compounds which yielded substitution products, 7 gave dixanthenyl derivatives as the sole products. Sulfanilamide itself, as expected, also yielded a disubstituted compound. Repetition of the preparation of all the derivatives employing a 2 to 1 molar ratio of xanthydrol to the sulfanilamide resulted in products identical with those previously obtained from an equimolar reaction. The data for the mono- and dixanthenyl derivatives are tabulated in Tables I to IV.

The infrared characteristics of the substitution products were typical of secondary amines, establishing the N^4-position as the site of substitution in the monoxanthenyl derivatives and as one of the sites in the disubstituted products. The parent sulfanilamides exhibited two bands in the NH stretching region (3 500 – 3 300 cm^{-1}) and an NH deformation band in the 1 640 – 1 590 cm^{-1} region, typical of primary aromatic amines. The substitution products, on the other hand, showed but a single band in the former region, and the latter band had either disappeared or was greatly reduced in intensity, diagnostic of secondary amines (Table V). The derivatives of sulfaphenazole (I*m*) and sulfaguanidine (IV*a*) were atypical in this respect. The presence of two bands in the NH stretching region for the latter derivative is likely due to the presence of other NH_2 groups in the molecule. In fact, the spectra of the dixanthenyl derivative of sulfaguanidine (IV*b*), isolated in a very low yield from the crude monoxanthenyl derivative, still displayed two bands in the NH stretching region, although the deformation band was

TABLE V

NH stretching and bending vibrations of parent sulfanilamides and their xanthenyl derivatives

	Compound	ν_{NH} (cm^{-1})		δ_{NH_2} (cm^{-1})	
		Parent	Derivative	Parent	Derivative
I*a*	Sulfanilamide	3 430, 3 305	3 333	1 630	—
I*b*	Sulfacetamide	3 478, 3 372	3 367	1 646	—
I*c*	Sulfaproxyline	3 431, 3 350	3 378	1 633	—
I*d*	Sulfanilanilide	3 367, 3 306	3 317	1 641	—
I*e*	Sulfadiazine	3 390, 3 310	3 279	1 653	—
I*f*	Sulfamerazine	3 442, 3 333	3 378	1 630	—
I*g*	Sulfamethazine	3 401, 3 300	3 333	1 644	—
I*h*	Sulfadimethoxine	3 390, 3 279	3 310	1 647	—
I*i*	N^1-Acetylsulfamethoxypyridazine	3 454, 3 356	3 378	1 655	—
I*j*	Sulfamethoxazole	3 413, 3 318	3 305	1 618 m*	1 618 w
I*k*	Sulfisoxazole	3 436, 3 322	3 344	1 631	—
I*l*	N^1-Acetylsulfisoxazole	3 436, 3 340	3 322	1 633	—
I*m*	Sulfaphenazole	3 390, 3 300	3 419, 3 317	1 631 s	1 629 m
II*a*	Sulfathiazole	3 279, 3 226	3 300	1 626	—
II*e*	Sulfamethizole	3 384, 3 284	3 340	1 645	—
II*f*	Sulfaethylthiadiazole	3 442, 3 322	3 344	1 639	—
III*a*	Sulfapyridine	3 384, 3 279	3 322	1 639 s	1 638 w
III*b*	Sulfisomidine	3 425, 3 322	3 311	1 634 m	1 639 vw
III*c*	Sulfachloropyridazine	3 472, 3 362	3 300	1 631	—
III*d*	Sulfamethoxypyridazine	3 448, 3 356	3 300	1 634	—
IV*a*	Sulfaguanidine	3 367, 3 305	3 367, 3 300	1 621 s	1 633 m†
I*n*	Metachloridine	3 390, 3 311	3 367	1 631	—
IV*d*	Ethyl-*p*-aminobenzoate	3 413, 3 311	3 350	1 639	—

*INTENSITIES: s = strong, m = medium, w = weak, and vw = very weak.
†This band is absent in the dixanthenyl derivative IV*b*.

now missing. Seydel (12) observed some anomalous results with sulfaphenazole (I*m*) which led him to conclude that it existed, at least in part, as 5-sulfanilimido-1-phenyl-2*H*-pyrazoline. It is probable, therefore, that the derivative obtained in this investigation may be a mixture of the N^4- and the 2-pyrazoline substituted products, with the former predominating. This would explain the weakly positive results obtained in the qualitative tests for free amino groups, as well as the fact that, although the elemental analysis was satisfactory, a recovery of only 95% was obtained on titration of this monoxanthenyl derivative.

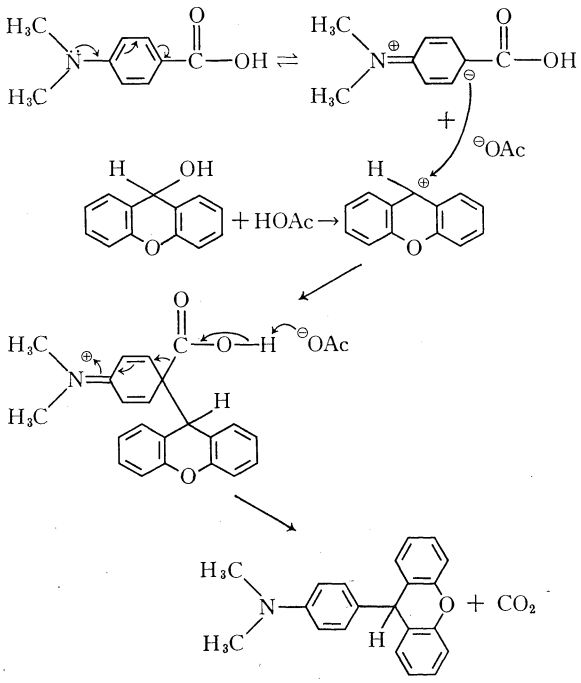
As mentioned above, Phillips and Frank (7) have postulated ring substitution for the xanthydrol derivative of sulfanilamide (I*a*). Their evidence in support of this conclusion consisted of a positive nitrous acid test for primary aromatic amines. Subjecting each of the derivatives prepared in this study to this test provided a positive result in each instance. However, negative results were obtained with both the furfural (13) and the sodium pentacyanoaquoferriate (14) tests for primary amines. A closer examination of the diazotization and coupling results revealed that the compounds were being decomposed in the acid solution, liberating some of the free amine, which accounted for the positive tests. Thus, the disubstituted product with sulfanilamide is correctly represented as N^1,N^4-dixanthenylsulfanilamide, and not 3,N^1-dixanthenylsulfanilamide as previously postulated (7).

Of the dixanthenyl derivatives prepared, only one, sulfadimethoxine (I*h*), was titratable as an acid. This indicated that, since the sulfonamide hydrogen atom was not involved in the derivative formation, ring substitution must have occurred. The only remaining hydrogen atom available for substitution was that in the 5-position of the pyrimidine ring. This position has been shown to be very reactive towards electrophilic substitution when the 2- and 4-positions are occupied by strongly ortho–para directive groups (15). In contrast, with sulfisomidine (III*b*), where the 2- and 4-positions are occupied by methyl rather than methoxy groups, substitution did not occur at the 5-position and only the monosubstituted N^4-xanthenyl derivative was obtained.

A similar behavior resulted from the bromination of the two parent sulfanilamides. Sulfadimethoxine (I*h*) yielded a tribromo derivative, whereas sulfisomidine (III*b*) is reported to give the normal corresponding 3,5-dibromosulfanilamide derivative (16). Condensation of the above tribromo compound, N^1-(2,6-dimethoxy-5-bromo-4-pyrimidyl)-3,5-dibromosulfanilamide, with xanthydrol failed to yield a product. This suggested that the two ortho bromine atoms sterically prevented substitution on the amino (N^4) group. In support of the above, *p*-aminobenzoic acid, when reacted with xanthydrol, yielded *N*-xanthenyl-*p*-aminobenzoic acid (IV*c*), whereas 3,5-dibromo-*p*-aminobenzoic acid failed to react. Similarly, whereas sulfacetamide (I*b*) gave the corresponding N^4-xanthenyl derivative, its 3,5-dibromo analogue did not react with the reagent. Finally, sulfaethylthiadiazole (II*f*) gave a dixanthenyl derivative; the brominated compound II*g* yielded only a monoxanthenyl derivative. This latter derivative, in contrast to all the other substitution products, was not decomposed by heat and was easily crystallized from ethanol. Isobuzole (II*h*), a structurally related analogue of sulfaethylthiadiazole, likewise gave a stable monoxanthenyl derivative.

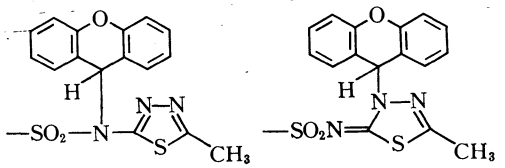
As expected, acylation of the amino group destroys its reactivity toward xanthydrol. Thus, *p*-acetamidobenzoic acid failed to react with xanthydrol. Succinyl- (II*b*) and phthalyl-sulfathiazole (II*c*) each yielded monoxanthenyl derivatives, as opposed to the disubstituted product obtained with sulfathiazole (II*a*) itself. *p*-Nitrosulfathiazole (II*d*) also provided a monoxanthenyl derivative. The above three compounds were all stable to normal recrystallization procedures. The preceding observations served to isolate the bond between the C^9-(xanthenyl) and the N^4-(sulfanilamide) groups as the linkage responsible for the instability of these compounds and, in addition, pointed to the stronger nature of the bond involving the second xanthenyl

[1]



radical. Like the amino group, the dimethylamino group failed to induce ring substitution in the ortho position. Treatment of *p*-dimethylaminobenzoic acid with xanthydrol yielded the decarboxylated substitution product *p*-(9-xanthenyl)-*N*,*N*-dimethylaniline. A plausible mechanism which would explain the reaction sequence leading to this product would appear to be that illustrated in reaction [1]. *p*-Dimethylaminobenzaldehyde, on the other hand, failed to react.

For sulfanilamides yielding dixanthenyl derivatives, acetylation in the N^1-position resulted in the corresponding monosubstituted derivatives. Thus, N^1-acetylsulfamethoxypyridazine (I*i*) and N^1-acetylsulfisoxazole (I*l*) each yielded the corresponding N^4-xanthenyl derivatives. This observation, coupled with the failure of the dixanthenyl derivatives to be titrated as acids, established the involvement of this hydrogen atom in the substitution by the second xanthenyl radical. Substitution of the amide hydrogen may be accounted for in one of two ways. Firstly, reaction may have occurred from the amido form at N^1, or secondly, substitution may have taken place from a tautomeric imido form. For example, with sulfamethizole, the partial structure of the resulting product would be that given by either II or III, respectively.



II III

These tautomeric forms were distinguished by an examination of the relative positions of the SO_2 symmetric stretching frequencies in the spectra of the derivatives. The difference in the S=O double-bond character between these two forms causes a shift to lower frequency of the band in the imido form relative to that in the amido form. In line with Uno's (17) findings, the 1 160 – 1 145 cm^{-1} and the 1 145 – 1 125 cm^{-1} regions have been assigned to the amido and imido forms, respectively. A comparison of the SO_2 symmetric stretching

TABLE VI

SO_2 symmetric stretching frequencies of sulfanilamides and their xanthenyl derivatives

	Compound	SO_2 stretching (cm^{-1}) Parent	Derivative
I*b*	Sulfacetamide	1 148	1 147
I*c*	Sulfaproxyline	1 151	1 151
I*e*	Sulfadiazine	1 153	1 148
I*f*	Sulfamerazine	1 147	1 147
I*g*	Sulfamethazine	1 144	1 152
I*h*	Sulfadimethoxine	1 142	1 152
I*j*	Sulfamethoxazole	1 154	1 159
I*m*	Sulfaphenazole	1 148	1 155
III*a*	Sulfapyridine	1 122	1 127
III*b*	Sulfisomidine	1 126	1 115
IV*a*	Sulfaguanidine	1 127	1 133*
II*e*	Sulfamethizole	1 126†	1 139‡
II*f*	Sulfaethylthiadiazole	1 140	1 140
II*g*	3,5-Dibromosulfaethylthiadiazole	1 143	1 142
II*h*	Isobuzole	1 159§	1 145
II*a*	Sulfathiazole	1 134	1 135
II*b*	Succinylsulfathiazole	1 142	1 140
II*d*	*p*-Nitrosulfathiazole	1 152	1 146
III*d*	Sulfamethoxypyridazine	1 153‖	1 133
III*c*	Sulfachloropyridazine	1 144	1 134
I*k*	Sulfisoxazole	1 159	1 147¶
I*i*	N^1-Acetylsulfamethoxypyridazine	1 155	1 151
I*l*	N^1-Acetylsulfisoxazole	1 156	1 160

*1 119 cm^{-1} in the dixanthenyl derivative IV*b*.
†Shoulder at 1 143 cm^{-1}.
‡1 135 cm^{-1} in chloroform.
§Shoulder at 1 139 cm^{-1}.
‖Weak band at 1 126 cm^{-1}.
¶Weak band at 1 159 cm^{-1}.

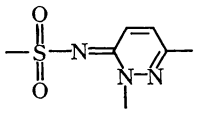
frequencies in the derivatives with those in the parent compounds is given in Table VI.

Compounds I*i* and I*l*, both of which have fixed amido structures, exhibited their frequencies well within the region assigned to this tautomeric form. Compounds III*a*, II*e*, and II*a*, which have been reported to exist in the imido form, displayed their frequencies in the assigned lower frequency region. The derivatives of the first eight compounds listed in Table VI showed their absorptions in the range of 1 159 – 1 147 cm^{-1} and, accordingly, they have been assigned the amido tautomeric form. Consistent with this interpretation, each of these derivatives was titratable as an acid. Sulfapyridine (III*a*) has been shown to exist in the imido form by several authors (17–19). The appearance of the SO_2 band in its N^4-xanthenyl derivative at almost the same position suggests that, in the solid state, this compound assumes the imido form. The comparably low frequencies in compounds III*b* and IV*a* imply an identical behavior, although similar data for the parent compounds are not available.

Reaction with the remaining 10 compounds in Table VI involved the hydrogen atom concerned in the prototropic tautomerism, since the derivatives were no longer titratable as acids. Sulfamethizole (II*e*) has been shown by Sheinker *et al.* (20) to exist in the imido tautomeric form. Its spectrum showed a strong SO_2 stretching absorption at 1 126 cm^{-1} with a well-defined shoulder at 1 143 cm^{-1}. This doublet became a sharp single band, appearing at 1 139 cm^{-1}, in the derivative. Because this latter frequency is still well within the imido region, the structure given in Table II can be assigned to its dixanthenyl derivative. On the basis of the close proximity

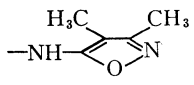
of this absorption in the succeeding three analogues (II*f*, II*g*, and II*h*), comparable imido structures have been assigned to their xanthenyl derivatives. For isobuzole (II*h*), it appears that the shoulder at 1 139 cm^{-1} represents the SO_2 symmetric stretching frequency in the parent compound, since it shows two well-defined maxima in the ultraviolet region, characteristic of the imido tautomeric form (19–21). Sulfathiazole (II*a*), which has been shown to exist in the imido form (17–20), displayed its SO_2 stretching frequency at 1 134 cm^{-1}. Since this absorption in its dixanthenyl derivative appeared at almost the same position, it has also been assigned the imido form. The comparably low frequency in the succinyl analogue II*b* was similarly interpreted as favoring this tautomeric form. The stretching frequency in the derivative of the *p*-nitro analogue II*d* occupied a borderline position, rendering interpretation difficult. Nonetheless, by analogy with the other members in the sulfathiazole series, the imido form would appear to be the most likely structure as well for this xanthenyl derivative.

Sulfamethoxypyridazine (III*d*) exhibited quite a substantial shift to lower frequency in going from the parent compound to the derivative. Although less dramatic, the same was true with the chloro analogue III*c*. Both of the parent compounds displayed but a single maximum in the ultraviolet region, indicative of the amido form. The low positions of the SO_2 symmetric stretching frequencies in the spectra of their derivatives suggested the imido form in both instances. Conducive to this tautomeric shift, both of these sulfonamides yielded highly colored products, as opposed to all the other sulfonamides, none of which showed any color change upon alkylation. The conjugated system (IV) established in each instance would account for this observation. Similar conjugated systems are not developed in the thiazole and thiadiazole series.

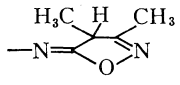


IV

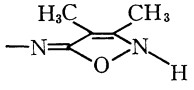
Sulfisoxazole (I*k*) appears to represent a unique situation not previously encountered in this study. The SO_2 symmetric stretching frequency at 1 159 cm^{-1}, coupled with only one maximum in the ultraviolet, suggests strongly that the parent compound assumes the amido form in the solid state. An apparent shift to lower frequency (1 147 cm^{-1}) occurred in its derivative, although a weak, clearly defined band also appeared at the same 1 159 cm^{-1} position. Assuming the stronger former band to be the true SO_2 symmetric stretching frequency in the derivative still poses a problem in interpretation because of its borderline position. Prototropic tautomerism in this sulfonamide differs from those previously encountered, because the annular nitrogen atom is now considerably removed from the extra-ring nitrogen. Three tautomeric forms are possible in this compound. Structure VI is the least likely possibility for the reactive form, because of the steric inaccessibility at this site. Reaction from the latter (VII) tautomeric form would establish a conjugated system, similar to that encountered with the pyridazine sulfanilamides, and accordingly would be expected to yield a colored xanthenyl derivative. Since no color change was evident, reaction would appear to have occurred from the amido (V) tautomeric form. Several reports in the literature tend to substantiate this conclusion. Boulton and Katritzky (22), from infrared and nuclear magnetic resonance studies, found that 5-amino- as well as 5-acetamido-isoxazoles existed predominantly in the amino (V) form. Enoki (23), from a study on the acetylation of sulfanilamides, found that sulfisoxazole, as opposed to other sulfanilamides, readily underwent selective acetylation at the N^1-position. This compound thus appears to represent a unique example



V



VI



VII

of N^1-substitution of a secondary sulfonamide by xanthydrol. This site represents the fourth distinct site of substitution encountered in this study.

Furthermore, it was found that acids even weaker than glacial acetic (pK_a = 4.76) were capable of protonating the hydroxyl group in xanthydrol and thus yielding the xanthylium ion (I). Sulfacetamide (pK_a = 5.38) and xanthydrol in 95% ethanol at room temperature gave an excellent yield of N^4-xanthenylsulfacetamide (I*b*). Sulfamethizole (pK_a = 5.45), when condensed with xanthydrol in ethanol, yielded a dixanthenyl derivative II*e* identical with that previously obtained by the general procedure. Similarly, *p*-aminobenzoic acid (pK_a = 4.68), under the same reaction conditions, gave *N*-xanthenyl-*p*-aminobenzoic acid (IV*c*). The considerably weaker acid sulfapyridine (pK_a = 8.43), on the other hand, failed to react in ethanol, yielding only starting material. The weakly basic urea failed to yield a product after being left for 1 month, but on the addition of acetic acid, dixanthenylurea separated within 30 min. The proposed nature of the reaction was substantiated by demonstrating the necessity of an ionizing solvent. Xanthydrol and sulfacetamide, allowed to stand in acetone for 1 month, failed to yield a product. Upon the addition of 95% ethanol to the mixture, the N^4-xanthenyl derivative I*b* separated after several days. The preceding results suggest that alkylation reactions with xanthydrol may be accomplished in the presence of acids even weaker than glacial acetic. Furthermore, they indicate that, with compounds possessing pK_a values of about 5.5 and being otherwise capable of condensing with xanthydrol, the reactions may proceed in ethanol without any added acid catalyst.

The ability of xanthydrol to yield its carbonium ion under such weakly acidic conditions indicates that the hydroxyl group in the former must be quite basic. The ease of formation of a carbonium ion from a carbinol in an acidic medium has been considered to reflect what has been termed the "secondary basicity" (24) of the carbinol (25). The expression of this basicity in terms of values of pK_{R^+}[1] provides a basis for comparison of carbinols. From a spectroscopic study of the equilibrium constant (K_{R^+}) in the reaction

$$R^+ + HOH \rightleftharpoons ROH + H^+,$$

Arnett and Bushick (26) obtained a pK_{R^+} value for xanthydrol of -0.17.[2] The secondary alcohol benzhydrol, by comparison, has been found to exhibit a much weaker "secondary basicity," yielding a value of -13.3 (28). Even the tertiary alcohol triphenylcarbinol ($pK_{R^+} = -6.44$)[3] (26) has been shown to be a much weaker base. This comparison may be carried further; in fact, both Deno *et al.* (28) and Arnett and Bushick (26) found xanthydrol to display the highest "secondary basicity" of all the carbinols studied, exclusive of 4,4′,4″-trimethoxytriphenylcarbinol ($pK_{R^+} = +0.82$). It has been shown that triphenylcarbinol is sufficiently less basic than xanthydrol that carbonium ion formation in glacial acetic acid for the former is negligible and results only after the addition of sulfuric acid (24).

The ease of formation of the xanthylium ion (I) suggests the likelihood of an inherent stability being associated with this ion. A comparison of the resonance forms for the carbonium ions resulting from xanthydrol, benzhydrol, and triphenylcarbinol revealed that 9 canonical structures can be drawn for xanthydrol, 7 for benzhydrol, and 10 for triphenylcarbinol. However, considering the relative contributions of these resonance forms, one must take into account the very significant contributions of the two oxonium ion structures to the stability of the xanthylium ion. Similar important contributors are not present in the carbonium ions of benzhydrol or triphenylcarbinol.

A Fisher–Hirschfelder–Taylor model of xanthydrol revealed this structure to be buckled, by virtue of the tetrahedral carbon atom in the 9-position. The xanthylium ion (I), on the other hand, proved to

[1]The negative logarithm of the equilibrium constant for the reaction.
[2]Also reported as -0.84 (27).
[3]Also reported as -6.63 (28).

be a planar structure, because of the trigonal nature of the carbon atom at this position. Similar studies with a model of the triphenylcarbinol carbonium ion revealed that all of the benzene rings could not be made to lie in a common plane. Such an arrangement must involve a loss of resonance stabilization, since maximum resonance stability is commonly associated with planarity. Since the xanthylium ion (I) is planar (stabilized by resonance) and is, in its electron composition, isoelectronic with anthracene, it must possess aromatic character. It is our contention, therefore, that the exceptional ease of formation of this carbonium ion is associated with the gain in stability accompanying the transformation, because of the aromatic character of the resulting ion.

The great stability of this carbonium ion was demonstrated by storing a solution of xanthydrol in glacial acetic acid for 2 months before its use in a condensation reaction. Equally good results were obtained from this solution as compared with a freshly prepared one. Phillips and Pitt (10) employed, for convenience, a stock solution of xanthydrol in acetic acid for preparing derivatives of primary amides. They reported no decomposition after periods as long as 4 months, and actually considered this reagent to be more stable in this form than in the dry state. Therefore, the exceptional reactivity of xanthydrol must be associated with the inimitable stability of the xanthylium ion, which in turn must be related to the aromatic character of this carbonium ion.

The results of this study suggest the applicability of xanthydrol as an alkylating agent for a variety of related aromatic amines, for example, metanilamides (I*n*) and *p*-aminobenzoate esters (IV*d*). In addition, they have revealed that certain secondary sulfonamides are capable of being alkylated by this reagent. However, for the former compounds, the instability associated with the C—N bond formed in these derivatives may also be predicted. Presently, similar studies are in progress, with other alcohols as alkylating agents (benzhydrol, triphenylcarbinol, and thiaxanthydrol).

EXPERIMENTAL

All melting points recorded in this investigation were taken on a Thomas–Hoover capillary melting point apparatus, and are uncorrected. Infrared spectra were recorded as Nujol mulls on a model 21 Perkin–Elmer infrared spectrometer. Ultraviolet spectra were obtained on a Beckman model DK-2 spectrometer. Elemental analyses were performed by Messrs. Weiler and Strauss, Oxford, England.

Xanthydrol was obtained as the commercial product from Eastman Kodak Co. Inc., New York. The *sulfanilamides* were either obtained commercially or were generous gifts of the manufacturers.

General Procedure for the Preparation of the 9-Xanthenyl Derivatives

To 1 g (0.005 mole) of xanthydrol in 15 ml of glacial acetic acid was added an equimolar amount of the sulfanilamide dissolved in a minimum volume (2–5 ml) of *N,N*-dimethylformamide while the mixture was stirred electromagnetically. Stirring was continued for 15 to 30 min beyond the time when the derivative first began to separate. The product was collected on a medium-porosity, sintered-glass funnel, washed well with cold ethanol, and dried in a vacuum desiccator over P_2O_5.

General Procedure for the Recrystallization of the Crude 9-Xanthenyl Derivatives

The crude derivative was dissolved in a minimum volume of pyridine (or other applicable solvent) at room temperature, and the resulting solution was filtered. Water (or *n*-hexane) was then added in small portions until the first sign of cloudiness or until crystal formation was evident; then the solution was set aside to allow for slow crystallization. After crystallization was complete, the product was collected on a medium-porosity, sintered-glass funnel, and washed several times with an appropriate mixture of the cold mixed solvents. The crystals were then dried in a vacuum desiccator over P_2O_5 and the melting point was recorded. The procedure was then repeated until a constant melting point had been attained.

Drying of Recrystallized Samples

Those derivatives that were recrystallized from pyridine–water or pyridine–hexane mixtures were treated as follows. To the recrystallized sample contained in a sintered-glass funnel, 20 ml of *n*-pentane was added; by use of a glass rod the sample was carefully reduced in particle size and mixed well with the solvent. The funnel was covered with a watch glass and the *n*-pentane allowed to drain from the sample under normal pressure. When the solvent had almost completely drained, a vacuum was applied for several minutes. The process was repeated until the odor of pyridine was no longer discernible (up to 20 washings). After this, the sample was dried in a drying pistol at room temperature

for 48 h. Those derivatives that were recrystallized from acetone or chloroform mixtures were subjected to only the latter treatment. The dry purified samples were then submitted for carbon, hydrogen, and nitrogen analyses.

Equivalent Weight Determinations

The derivatives were titrated nonaqueously by employing a modification of the method of Vespe and Fritz (29), which has been reported previously (30).

3,5-Dibromo-4-aminobenzoic Acid

This was prepared by an adaptation of a bromination method described for phenols (31). To 1 g of *p*-aminobenzoic acid in a minimum of ethanol, brominating solution (15 g of KBr in 100 ml of water plus 10 g of bromine) was added dropwise, with constant stirring. The yellow color continued to disappear until finally a white product separated. The addition of the brominating solution was continued until no more product precipitated. A 50 ml portion of water was added, and the product was filtered off and washed with a dilute solution of sodium bisulfite followed by water. One recrystallization from ethanol yielded a white product which did not melt below 300° (lit. unmelted at 280° (32)). Condensation with xanthydrol, by the general procedure, yielded only the starting acid.

p-Dimethylaminobenzoic Acid

This was prepared by a modification of the method described by Décombe (33). Silver oxide was prepared by adding a solution of 15 g (0.089 mole) of silver nitrate in 30 ml of water to a solution of 7 g (0.175 mole) of sodium hydroxide in 30 ml of water according to the procedure of Campaigne and LeSuer (34). This resulted in a very thick mixture which could not be stirred properly; hence, a further 90 ml portion of water was added to permit adequate agitation. To this mixture was added 6.3 g (0.0425 mole) of *p*-dimethylaminobenzaldehyde in small portions, with continuous stirring. After the addition was complete, the mixture was stirred for a further 30 min. The black silver suspension was removed by suction filtration and washed with four 25 ml portions of hot water. The cold combined filtrate and washings were acidified with glacial acetic acid, precipitating 5.94 g (85%) of *p*-dimethylaminobenzoic acid. After one recrystallization from 95% ethanol, the acid melted at 233–236° (lit. m.p. 235–238° (33)).

Reaction of p-Dimethylaminobenzoic Acid with Xanthydrol

To 1 g (0.005 mole) of xanthydrol in 15 ml of glacial acetic acid was added 0.83 g (0.005 mole) of *p*-dimethylaminobenzoic acid in 4 ml of *N,N*-dimethylformamide. Stirring was continued for 18 h, after which a white product had separated. The mixture was allowed to stand for a further 24 h, filtered, and washed well with cold ethanol. Further yields were recovered from the mother liquor, giving a combined yield of 0.6 g (35%). Six recrystallizations from ethanol yielded a white product melting at 155–156° which proved to be *p*-(9-xanthenyl)-*N,N*-dimethylaniline.

Anal. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.96; H, 6.29; N, 4.70.

p-(9-Xanthenyl)-N,N-dimethylaniline

This was prepared according to the method described by Adriani (9) by the reaction of xanthydrol with *N,N*-dimethylaniline. Recrystallization from ethanol yielded the title compound melting at 156–157.5° (lit. m.p. 157–158° (35)). This product did not depress the melting point when mixed with the compound isolated from the preceding reaction, and exhibited an identical infrared spectrum.

N-Acetyl-p-toluenesulfonamide

This compound was prepared by the method of Kemp and Stephen (36). The product, after crystallization from water, melted at 140–141.5° (lit. m.p. 137° (crystallized from ethanol) (36)). A mixture melting point with *p*-toluenesulfonamide (m.p. 138–140°) showed a large depression.

N^1-Acetyl-3,5-dibromosulfanilamide

This was prepared by the bromination of sulfacetamide, employing the method described previously for preparing 3,5-dibromo-4-aminobenzoic acid. One recrystallization from ethanol yielded white, rosette-shaped crystals melting at 191.5–192.5° (lit. m.p. 193.8–194.6° (2)); molecular weight: calculated 372.1, found 373.6 (nonaqueous titration). Condensation with xanthydrol, by the general procedure, failed to yield a product.

N^1-(2,6-Dimethoxy-5-bromo-4-pyrimidyl)-3,5-dibromosulfanilamide

This was prepared by the bromination of sulfadimethoxine according to the method described above, except that acetone rather than ethanol was used as the solvent. One recrystallization from ethanol yielded a product melting at 190–191°; molecular weight: calculated 547.1, found 548.6 (nonaqueous titration). Treatment with xanthydrol, by the general method, gave only the unreacted sulfonamide.

N^1-(5-Ethyl-1,3,4-thiadiazol-2-yl)-3,5-dibromosulfanilamide

This was similarly prepared by the bromination of sulfaethylthiadiazole, employing the method described previously for preparing 3,5-dibromo-4-aminobenzoic acid. Recrystallization from 70% ethanol yielded a white product melting at 146–147°, with previous softening (lit. m.p. 197° (37)).

Color Tests for the Detection of Primary Aromatic Amines

(a) Diazotization and Coupling

The quantitative procedure of Bratton and Marshall (38) was modified and applied in a qualitative capacity. To approximately 0.5 mg of the compound in several drops of *N,N*-dimethylformamide was added 5 ml of 0.5 *N* HCl followed by 5 ml of 0.1% sodium nitrite. If a precipitate formed after the addition of the hydrochloric acid, sufficient *N,N*-dimethylformamide was added to redissolve the precipitate. After 3 min, 5 ml of 0.5% ammonium sulfamate followed by 5 ml of 0.1% *N*-(1-naphthyl)-ethylenediamine dihydrochloride was added to the

clear solution. An immediate violet color was produced with each of the derivatives tested, as well as with the parent sulfanilamides. A blank run treated in exactly the same manner remained colorless upon the addition of the coupling reagent.

(b) Furfural

The color test with furfural was performed as described by Hucknall and Turfitt (13). The parent sulfanilamides each produced a violet color. The N^4-xanthenyl derivatives, on the other hand, remained colorless, except for the derivatives of sulfaphenazole (I*m*), which showed a faint violet color.

(c) Sodium Pentacyanoaquoferriate

This test was carried out by a modification of the method described by Anger (14). A small amount of the compound was placed on a spot plate, and acetone (a few drops) was added to dissolve the compound. One drop of the reagent solution, prepared by irradiating a 1% solution of sodium nitroprusside for 15 min under ultraviolet light, was added and the color was noted. The parent sulfanilamides yielded a mauve or green color, whereas the N^4-xanthenyl derivatives gave an orange color.

Effect of 0.5 N HCl on N^4-(9-Xanthenyl)-N^1-acetylsulfanilamide (Ib)

To 0.5 mg of the compound in a few drops of *N,N*-dimethylformamide was added 5 ml of 0.5 *N* HCl as described under section *a* above. Evaporation of the solvent yielded a residue which gave a positive test with furfural. A similar result was obtained when the solution was first neutralized with dilute sodium hydroxide and then evaporated to dryness.

N^4-(9-Xanthenyl)-N^1-acetylsulfanilamide (Ib)

This was obtained from the condensation of xanthydrol with sulfacetamide in 95% ethanol. Xanthydrol (1.84 g, 0.0093 mole) and sulfacetamide (2.0 g, 0.0093 mole) were dissolved in 40 ml of ethanol, and the resulting solution was filtered. The product began separating during the filtration process and, when isolated, weighed 1.75 g (48%). Two recrystallizations from pyridine–water at room temperature yielded a product melting at 207–208°. A mixture melting point with an authentic sample of the title compound, prepared by the general method, showed no depression. The infrared spectra were identical.

2-(N^4-(9-Xanthenyl)-sulfanilimido)-3-(9-xanthenyl)-5-methyl-Δ^4-1,3,4-thiadiazoline (IIe)

This was obtained from the reaction of xanthydrol with sulfamethizole in 95% ethanol. To 1 g (0.005 mole) of xanthydrol in 30 ml of ethanol was added 0.68 g (0.0025 mole) of sulfamethizole in the dry state. Sufficient ethanol was added to yield a clear solution. Leaving the mixture overnight gave 0.91 g (57%) of a white product melting at 198–200°. Three recrystallizations from chloroform–*n*-hexane followed by two from acetone–water, each at room temperature, raised the melting point to 206.5–207°. The resulting derivative exhibited physical properties identical with those of an authentic sample of the title compound prepared earlier by the general method.

N-(9-Xanthenyl)-p-aminobenzoic Acid (IVc)

This compound was recovered, in a very low yield, from the reaction of *p*-aminobenzoic acid with xanthydrol in 95% ethanol. To 1 g (0.005 mole) of xanthydrol in 25 ml of ethanol was added 0.7 g (0.005 mole) of *p*-aminobenzoic acid in 10 ml of ethanol. After 2 weeks at room temperature, a small amount of a white product separated which was shown by its physical properties to be identical with the title compound.

Attempted Condensation of Sulfapyridine with Xanthydrol in Ethanol

The mixing of equimolar portions of the above reactants, each in a minimum volume of ethanol, failed to yield a product. Only a small amount of the parent sulfanilamide was recovered.

N^4-(9-Xanthenyl)-N^1-acetylsulfanilamide (Ib)

Equimolar portions (0.005 mole) of xanthydrol and sulfacetamide were dissolved in a minimum volume of acetone, and the resulting solution was filtered. After 1 month at room temperature, the solution remained clear. To this solution was added 25 ml of 95% ethanol, and the mixture was again left undisturbed. After several days a white crystalline product (the title compound) melting at 205–207° had separated. A mixture melting point with an authentic sample of the title compound showed no depression.

N,N^1-Dixanthenylurea

To 1 g (0.005 mole) of xanthydrol in 40 ml of ethanol was added 0.15 g (0.0025 mole) of urea dissolved in a minimum volume of ethanol. One month at room temperature failed to yield a product. At this point, 10 ml of glacial acetic acid was added to the mixture, with continuous stirring. After 25 min, a white product (the title compound) melting at 250–251° had separated (lit. m.p. 250–258° (39)).

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