ALKYL AND ARYLSULFONYL DERIVATIVES OF ORTHO-AMINOPHENOLS

BY L. CHAS. RAIFORD AND OLIVER GROSZ

In previous work in this Laboratory it has been shown that, in general, only one acetylbenzoyl derivative of an *o*-aminophenol can be obtained, regardless of the order in which the acyl radicals are introduced, and that in this product the benzoyl radical is attached to nitrogen. To meet this requirement the migration of acyl from nitrogen to oxygen must have occurred in one of these reactions. The fact that this migration is not prevented by the presence of heavy radicals attached to the nucleus of the aminophenol, and that it occurs when *o*-aminophenol is replaced by 1-amino-2-naphthol and by 1-amino-8-naphthol indicates that this behavior is probably general for this class of compounds when the acyl radicals are those specified.[1] More recent work by Lankelma and Knauf[2] shows that with these acyl radicals no rearrangement occurs upon acylation of the N-acyl derivative of *o*-aminothiophenol. Hydrolysis of 2-acetylamino-4-chlorophenyl thiobenzoate causes a migration of benzoyl from sulfur to nitrogen.

A second point of interest in these studies was the attempt to determine which factors influence this migration most noticeably, and in this connection it was shown that in the greater number of cases the heavier and more acidic radical was found attached to nitrogen, and that while migration usually occurred during acylation it might take place during hydrolysis in some instances. Similar results were obtained with a number of other pairs of acyl radicals when both were of the structure $O{=}\overset{|}{C}{-}R$ (Ph). When one was of the structure $O{=}\overset{|}{\underset{\underset{Ph}{|}}{S}}{=}O$, no rearrangement was observed anywhere in the cycle.[3]

In the previous study only a few observations were made with radicals containing the sulfonyl group; consequently, it was desired to test the question further. In the work now reported there were prepared derivatives in which the acyls differed in weight and acidity to a much greater degree than in the cases already tested, and where one of them always contained the sulfonyl group.[4]

[1] Raiford and Clark, THIS JOURNAL, **48**, 483 (1926). This paper contains important references to other work.

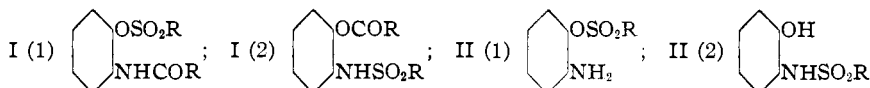[2] Lankelma and Knauf, *ibid.*, **53**, 309 (1931).

[3] Raiford and Lankelma, *ibid.*, **47**, 1111 (1925).

[4] While the present work was in progress, Bell [*J. Chem. Soc.*, 1981 (1930)] reduced

Another consideration in the present work was the desire to test the effect of the carbalkoxy radical. Ransom[5] found that the reaction of 2-benzoylaminophenol with ethyl chlorocarbonate and that of 2-hydroxyphenylurethan with benzoyl chloride gave the same product, and the latter was shown to be 2-benzoyloxyphenylurethan. From this and later work, Ransom and Nelson[6] concluded, (1) "that when two carboxyl radicals (COOR and COOR₁) are introduced into the molecule of o-aminophenol, the lighter one becomes attached to nitrogen, the positions not being influenced by the order in which the groups are introduced; (2) that this is also true when both of the radicals are carbonyls (COR and COR₁); (3) and in case one radical is carbonyl and the other carboxyl, the latter becomes attached to nitrogen without being influenced by the relative weights of the entering groups." Although work at Iowa has definitely shown that, in general, conclusion (2) does not hold, it was desired to test both (2) and (3) with derivatives in which one or both acyl radicals contain the sulfonyl group.

TABLE I

REPULSION ENERGIES FOR DIFFERENT LINKAGES

Compound	Linkage	Kernel charges e	e'	Dist. bet. atomic centers,[a] Å., d	$E = ee'/d$	Repulsion energy in kilocalories $= E \times 330.3$[b]	Sum	Difference
I (1)	O—S	6	6	1.67	21.56	7120		
	N—C	5	4	1.47	13.61	4494	11614	
I (2)	O—C	6	4	1.42	16.90	5583		269
	N—S	5	6	1.72	17.44	5762	11345	
II (1)	O—S	6	6	1.67	21.56	7120		
	N—H	5	1	1.15	4.35	1436	8556	
II (2)	O—H	6	1	1.05	5.72	1887		907
	N—S	5	6	1.72	17.44	5762	7649	

I (1) [benzene ring with OSO₂R and NHCOR]; I (2) [benzene ring with OCOR and NHSO₂R]; II (1) [benzene ring with OSO₂R and NH₂]; II (2) [benzene ring with OH and NHSO₂R]

[a] Huggins, *Phys. Rev.*, **28**, 1086 (1926); Latimer, THIS JOURNAL, **51**, 3185 (1929).

[b] Some of these repulsion energies were previously calculated by Latimer, who obtained only half the above values. Those here recorded were calculated according to Pauling and Hendricks [THIS JOURNAL, **48**, 641 (1926)] and are believed to be correct.

2-nitrophenyl p-tolylsulfonate and found the chief product to be the corresponding 2-aminophenyl derivative, which was stable and which showed no tendency to rearrange to the N-acyl compound. Several mixed diacyl derivatives of o-aminophenol in which one radical contained a sulfonyl group were prepared. In every case the radical first introduced went to nitrogen. However, attempts to prepare the isomeric substances were not always carried out. In the cases studied, rearrangement occurred neither during acylation nor during hydrolysis.

[5] Ransom, *Ber.*, **31**, 1059 (1898).

[6] Ransom and Nelson, THIS JOURNAL, **36**, 393 (1914).

In this connection it is important to study another viewpoint. Recently Latimer[7] proposed a theory that "if there are a number of possible arrangements of the atoms in a molecule which have the same number of electrons per atom, and which satisfy equally well the tendencies of the more electronegative elements to complete their octets of electrons, that form will be the most stable which gives a minimum of repulsion between the atomic kernels." Since the author states that this theory is valid for most reactions in which a molecular rearrangement takes place, it is interesting to consider what it predicts in those cases where one of the acyl radicals contains a sulfonyl group. The energy of repulsion is $E \times 330.3$ kilocalories, and E can be calculated from the Formula $E = ee'/d$ where e and e' are the charges on the kernels and d is the distance between them. It will be seen from Table I that, in accordance with this theory, derivative (2) in each case represents that isomer in which the repulsion energy is least and which should be the most stable one of the pair. This would indicate that (1) should rearrange into (2). The present work, as well as that previously recorded, shows that both isomers are stable.

Experimental Part

The o-aminophenol used in these experiments was 2-amino-4-methyl-6-bromophenol. To obtain it, p-cresol was converted into the 2,6-dibromo derivative (OH = 1) by a modification[8] of the methods employed by Zincke and Wiederhold,[9] and Anderson;[10] the nitro group was introduced in place of one bromine atom by means of the Zincke[11] method,[12] and the resulting product was reduced to the corresponding amino compound.

TABLE II

EFFECT OF TEMPERATURE AND CONCENTRATION OF NITRATING AGENT

Expt.	Dibromocresol, g.	Sodium nitrite, g.	Temp., °C.	Yield, %
1	133	37[a]	18[b]	36
2	133	37	16	53
3	133	60	14	61
4	133	65	14	69
5	133	70	14	68

[a] Theory requires 34.5 g. [b] Zincke does not specify the temperature at which he worked.

[7] Latimer, THIS JOURNAL, 51, 3185 (1929).

[8] This consisted in the use of powdered iron as catalyst, and separation of the dibromocresol by distillation with steam.

[9] Zincke and Wiederhold, Ann., 320, 202 (1902).

[10] Anderson, J. Biol. Chem., 26, 393 (1916).

[11] Zincke, J. prakt. Chem., [2] 61, 563 (1900).

[12] In the use of this method it was found that the yield of product was influenced noticeably by the amount of nitrite and the temperature, as shown in Table II. In the experiments indicated one-half a gram molecular proportion of the dibromocresol was dissolved in a suitable amount of glacial acetic acid, and the reaction completed by the use of different amounts of sodium nitrite at the temperatures indicated.

The sulfonyl chlorides used in this work are on record, and were usually prepared by the interaction of the required sulfonic acid and phosphorus pentachloride. That one obtained from 2-chloro-5-nitrobenzenesulfonic acid, in accordance with P. Fischer's[13] method was of particular interest. It was purified by slow evaporation of its ether solution and was deposited in the form of large hexagonal plates, m. p. 89–90.° This substance emitted sparks during crystallization, and also when the bottle containing the dry solid was shaken in the dark. The yield of purified material was 75%. Fischer recorded no yield and ⋅d not note the sparking phenomenon.

The diacyl derivatives were frequently prepared by Einhorn and Hollandt's[14] method of treatment of the pyridine solution of the aminophenol or its hydrochloride with two molecular proportions of the required acid chloride. In some instances the best results were obtained by the Schotten–Baumann[15] method.

The N-acyl derivatives were sometimes prepared by the Einhorn and Hollandt method by the use of one molecular proportion of acid chloride. They were frequently obtained by hydrolysis of the corresponding diacyl derivative. With compounds containing acyl radicals of low molecular weight, hydrolysis could usually be brought about by aqueous alkali in the cold or by gentle warming, while those with high molecular weights required alcoholic alkali and, in a few cases, heating for some time.[16] When the acyl was represented by the carbalkoxy radical the derivative was prepared by Groenvik's[17] method.

A summary of the data secured by study of the action of several pairs of acyl radicals on 2-amino-4-methyl-6-bromophenol is given in Table III.

TABLE III

COMPOSITION AND BEHAVIOR OF DIACYL DERIVATIVES FROM
2-AMINO-4-METHYL-6-BROMOPHENOL

Pairs of acyl radicals	Character of derivative	Hydrolysis products
Benzoyl–Benzenesulfonyl	Different[a]	Normal[b]
Acetyl–Benzenesulfonyl	Different	Normal
Benzoyl–Carboethoxy	Identical	Carboethoxy on nitrogen
Carboethoxy–Benzenesulfonyl	Different	Normal
Benzenesulfonyl–β-Naphthalenesulfonyl	Different	Normal

[a] The term "different" refers to the fact that isomeric diacyl derivatives were obtained depending on the order in which the acyl radicals were introduced. [b] The term "normal" indicates that no rearrangement occurred on hydrolysis.

[13] P. Fischer, Ber., 24, 3196 (1891).

[14] Einhorn and Hollandt, Ann., 301, 101 (1898).

[15] Schotten–Baumann, Ber., 17, 2544 (1884); 19, 3218 (1886).

[16] The insolubility and tendency toward inactivity of compounds of high molecular weight has been noted by E. Fischer and collaborators in their study of tannin-like materials [ibid., 46, 3268 (1913)].

[17] Groenvik, Bull. soc. chim., [2] 25, 177 (1876).

This shows that when one of the radicals contained a sulfonyl group, isomeric derivatives were obtained when the radicals were introduced in different orders, and that no migration occurred during acylation or hydrolysis. Rearrangement occurred in that case only where neither acyl radical contained the sulfonyl group.

The use of an unsubstituted base gave similar results. Treatment of an aqueous potassium hydroxide solution of 2-hydroxyphenylurethan (prepared from 2-aminophenol) with benzenesulfonyl chloride gave a solid which after two crystallizations from ligroin melted at 78.5–79.° The yield of purified product was 58%.

Anal. Subs., 0.1454: BaSO₄, 0.1022. Calcd. for $C_{15}H_{15}O_5NS$: S, 9.98. Found: S, 9.66.

When 2-benzenesulfonylaminophenol was treated with ethyl chlorocarbonate, an oil was obtained. This was separated and dried for thirty days under partial vacuum, but remained liquid and was not obtained entirely pure. This seems to indicate that different products are formed when the acyl radicals here involved are introduced in opposite orders into the aminophenol, and that no rearrangement occurs.

It is interesting to note the effect of highly acidic substituents in the *o*-aminophenol. Though halogen atoms[18] do not prevent the formation of N-acyl-O-acyl derivatives, and the characteristic migration takes place when the acyls are acetyl and benzoyl, in the present work no diacyl derivative of 2-amino-4,6-dinitrophenol was obtained.

The accompanying tables give the physical constants and analytical data for the greater number of derivatives obtained in this work.

TABLE IV
N-ACYL DERIVATIVES OF 2-AMINO-4-METHYL-6-BROMOPHENOL

Substituted amino	Yield, %	Formula	M. p., °C.	Halogen, %[a] Calcd.	Found
Benzenesulfonyl-	80	$C_{13}H_{12}O_3NBrS$	157[b]	23.36	23.45
Carboethoxy-	84	$C_{10}H_{12}O_3NBr$	83	29.16	29.52
Naphthalenesulfonyl-	..	$C_{17}H_{14}O_3NBrS$	174.5[c]	20.38	20.06
Carbomethoxy-	..	$C_9H_{10}O_3NBr$	112–112.5[d]	30.74	30.82

[a] Analyses were made by the Carius method. [b] This product had the same melting point as the N-benzenesulfonyl-O-acetyl derivative, from which it was obtained by hydrolysis. A mixture of the two melted at 118–125°. [c] Crystallization from benzene gave nearly colorless needles. [d] Small cream-colored needles from dilute alcohol.

TABLE V
DIACYL DERIVATIVES OF 2-AMINO-4-METHYL-6-BROMOPHENOL

Names and positions of radicals	Yield (N. q. = nearly quantitative)	Formula	M. p., °C.	Halogen, % Calcd.	Found
N-Benzoyl-O-benzoyl	N. q.	$C_{21}H_{16}O_3NBr$	166[a]	19.49	19.81
N-Benzenesulfonyl-O-benzenesulfonyl	N. q.	$C_{19}H_{16}O_5NBrS_2$	230[b]	16.57	16.25

[18] Raiford and Woolfolk, THIS JOURNAL, **46**, 2246 (1924).

TABLE V   (*Concluded*)

Names and positions of radicals	Yield (N. q. = nearly quantitative)	Formula	M. p., °C.	Halogen, % Calcd.	Found
N-Benzoyl-O-benzenesulfonyl	97	$C_{20}H_{16}O_4NBrS$	114^c	17.91	17.87
N-Benzenesulfonyl-O-benzoyl	N. q.	$C_{20}H_{16}O_4NBrS$	172^d	17.91	18.10
N-Acetyl-O-benzenesulfonyl	79	$C_{15}H_{14}O_4NBrS$	116–116.5^e	20.81	21.18
N-Benzenesulfonyl-O-acetyl	N. q.	$C_{15}H_{14}O_4NBrS$	156–157^e	20.81	20.18
N-Carboethoxy-O-benzoyl	97	$C_{17}H_{16}O_4NBr$	142^f	21.14	21.20
N-Carboethoxy-O-benzenesulfonyl	73	$C_{16}H_{16}O_5NBrS$	115–115.5^g	19.30	19.33
N-Benzenesulfonyl-O-carboethoxy	N. q.	$C_{16}H_{16}O_5NBrS$	144–145^h	19.30	19.53
N - β - Naphthylenesulfonyl - O - β - naphthalenesulfonyl	N. q.	$C_{27}H_{20}O_5NBrS_2$	141–142^i	13.73	14.10
N - Benzenesulfonyl - O - β - naphthalenesulfonyl	40^r	$C_{23}H_{18}O_5NBrS_2$	123^j	15.02	15.89
N - β - Naphthalenesulfonyl - O - benzenesulfonyl	60^r	$C_{23}H_{18}O_5NBrS_2$	126^k	15.02	14.86
N - Carbomethoxy - O - (2 - chloro - 5 - nitrobenzene)-sulfonyl	94	$C_{15}H_{12}O_7N_2ClBrS$	151^l	24.06	23.96
N - (2 - chloro - 5 - nitrobenzene)sulfonyl - O - (2-chloro-5-nitrobenzene)sulfonyl	74^r	$C_{19}H_{12}O_9N_3Cl_2BrS_2$	221^m	23.53	23.37
N-Butanesulfonyl-O-butanesulfonyl	75^r	$C_{15}H_{24}O_5NBrS_2$	78.5^n	18.08	18.25
N-(3-nitro-4-methylbenzene)sulfonyl-O-(3-nitro-4-methylbenzene)sulfonyl	75^r	$C_{21}H_{18}O_9N_3BrS_2$	175–176°	13.31	13.48
N - (4 - bromobenzene)sulfonyl - O - (4 - bromobenzene)sulfonyl	59^r	$C_{19}H_{14}O_5NBr_3S_2$	130–131^p	37.36	37.46
N - (3,4 - dichlorobenzene)sulfonyl - O - (3,4 - dichlorobenzene)sulfonyl	80^r	$C_{19}H_{12}O_5NCl_4BrS_2$	114^q	35.77	36 30

^{a} Needles from a mixture of chloroform and ligroin. ^{b} Clusters of needles from alcohol. ^{c} Nearly colorless needles from alcohol. ^{d} Crystallization from alcohol gave nearly colorless prisms. ^{e} Both products separated as oils that crystallized upon standing.   From alcohol the N-acetyl derivative gave colorless prisms; the isomeric O-acetyl compound gave pale yellow prisms. ^{f} Fine, felt-like needles from alcohol. ^{g} Obtained in colorless needles from alcohol. ^{h} Crystallization from alcohol gave small colorless prims. ^{i} Small, colorless prisms from a mixture of alcohol and chloroform. ^{j} The oil first obtained was extracted with ether, the solution dried with anhydrous sodium sulfate, the ether distilled off, and the residue crystallized from alcohol. ^{k} Purified by crystallization from alcohol.   A mixture of this and the immediately preceding product had a melting range of 106–111°. ^{l} Crystallization from alcohol gave clusters of fine needles that radiated from a common center, and had the appearance of felt. ^{m} Small yellow prisms from acetone. ^{n} The oil that separated at first solidified on standing.   Crystallization from alcohol gave coarse colorless prisms. ^{o} Fine colorless needles from a mixture of alcohol and chloroform. ^{p} Small prisms from alcohol. ^{q} Coarse colorless prims from alcohol. ^{r} These figures represent the yields of purified products.

Summary and Conclusions

1.   2-Amino-4-methyl-6-bromophenol forms only one mixed diacyl derivative with the benzoyl and carboethoxy radicals, regardless of the order in which these groups are introduced, which is in accord with the behavior of these radicals toward other ortho aminophenols.

2.   The present work indicates that when one of the acyl radicals contains the sulfonyl group and the other the carbonyl or carboxyl group, isomeric diacyl derivatives will be obtained, depending on the order in which the radicals are introduced.   The isomers give normal results on

hydrolysis. These statements hold, also, when both radicals contain the sulfonyl group.

3. The results of the present study indicate that the repulsion energy of atomic kernels cannot be the sole factor in the migration of acyl radicals between nitrogen and oxygen in an ortho aminophenol derivative.

4. Attempts to prepare diacyl derivatives from 2-amino-4,6-dinitrophenol were unsuccessful.

5. Further work is in progress.

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[CONTRIBUTION FROM THE INSECTICIDE DIVISION OF THE BUREAU OF CHEMISTRY AND SOILS]

ROTENONE. XIV. THE RELATION OF THE OPTICAL ACTIVITY OF SOME ROTENONE DERIVATIVES TO THE STRUCTURE OF TUBAIC ACID

BY H. L. HALLER AND F. B. LAFORGE

In the early stages of the investigations on the structure of rotenone, it was found that the compound is decomposed by alcoholic potassium hydroxide, yielding tubaic acid[1] ($C_{12}H_{12}O_4$) in variable but small quantities. Considerable work has been done on this decomposition product, especially by the Japanese investigators, and it seems fairly well established that tubaic acid contains an indifferent (ether) oxygen atom as well as an hydroxyl group, in addition to the carboxyl group and an isoallyl side chain which can be reduced to the isopropyl group. The isomerization of tubaic acid is due to the shifting of a double bond,[2] forming the isopropyl group. This change is apparently the same as that which takes place when rotenone is isomerized to isorotenone.

Except for this one reaction, tubaic and isotubaic acids show none of the typical reactions of rotenone or isorotenone, and the question as to whether the nucleus of tubaic acid is actually present in rotenone, as is assumed by Takei and his co-workers[3] is one of considerable importance.

For a number of reasons we are inclined to reject this assumption. The first and most important reason for our objection is the fact that derritol, which beyond any doubt has the formula $C_{21}H_{22}O_6$, yields tubaic and isotubaic acid, as does rotenone and many other of its derivatives. In derritol all six of the oxygen atoms have been definitely characterized.

[1] T. Kariyone, V. Kimura and K. Kondo, J. Pharm. Soc. (Japan) No. 514, 1094 (1924); ibid., No. 518; 377 (1925); S. Takei, Ber., 61, 1003 (1928).

[2] A. Butenandt and F. Hildebrandt, Ann., 477, 245 (1930); S. Takei, M. Koide and S. Miyajima, Ber., 63, 1369 (1930).

[3] S. Takei, S. Miyajima and M. Ono, ibid., 64, 1000 (1931).