TABLE II

PROPERTIES AND DERIVATIVES OF METHYL-*t*-BUTYLACETOPHENONES

Acetophenone	B.P., °C./20 Mm.[a]	T_f, °C.	Purity, Mole %	Semicarbazone, M.P., °C.		Derived Benzoic Acid			
						M.P., °C.		Equiv. Wt.	
				Found	Lit.	Found	Lit.	Found	Calc'd
2-Methyl-4-*t*-butyl-	146	11.90	99.0–99.4	195–196	197[5]	142–143	143–144[5]	192.6	192.3
2-Methyl-5-*t*-butyl-	146	30.72	99.4–99.8	180–181	183[4]	98–99	101[5]	192.7	192.3
3-Methyl-5-*t*-butyl-	148	46.14[b]	99.0–99.5	177–178	...	163–164	162[14]	192.0	192.3

[a] Uncorrected. [b] Reported m.p. 47°.[14]

A mixture of 90 g. (0.47 mole) of 3-methyl-5-*t*-butylacetophenone, 71 g. (0.64 mole) of semicarbazide hydrochloride, 95 g. (1.2 moles) of sodium acetate, 280 ml. of water, and 350 ml. of ethanol was refluxed for 1 hour. The solution was cooled to room temperature and filtered. The solid was crystallized 5 times from ethanol to give 50 g. (43% yield) of semicarbazone; m.p. 177–178°, white needles.

Anal. Calc'd for $C_{14}H_{21}N_3O$: N, 16.99. Found: N, 16.69.

The semicarbazone was hydrolyzed by refluxing for 1 hr. with 400 ml. of 20% hydrochloric acid, and the regenerated ketone was extracted with ether. Distillation of the concentrated ether extract through a 27-plate column at 5/1 reflux ratio gave 35 g. (91% yield) of 3-methyl-5-*t*-butylacetophenone; b.p. 148°/20 mm., t_f 46.14° (99.0–99.5 mole % pure).

Anal. Calc'd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 81.94; H, 9.71.

Hydrobromite oxidation of dialkylacetophenones. The structures of the dialkylacetophenones (99+ mole % pure) were established by oxidation to known dialkylbenzoic acids. The general procedure follows: To a stirred, 0–10° mixture of 150 ml. of 5% aqueous sodium hydroxide and 10 g. (0.13 mole) of bromine was added 4.0 g. (0.02 mole) of dialkylacetophenone during 1 hr. The mixture was subsequently stirred for 9 hr. at 60°. The reaction mixture was cooled and extracted with ether to remove residual ketone. The aqueous layer was acidified and extracted with ether. The extract of the aqueous layer was concentrated and the solid residue was crystallized or sublimed to give about a 75% yield of methyl-*t*-butylbenzoic acid.

Nonisomerization of methyl-t-butylacetophenones. A mixture of 10 g. (0.05 mole) of 2-methyl-4-*t*-butylacetophenone (99.0–99.4 mole % pure), 10 g. (0.08 mole) of aluminum chloride and 100 ml. of carbon tetrachloride was stirred at 30° for 3 hr., then poured into an ice–hydrochloric acid mixture. The organic layer was washed successively with water, 5% aqueous sodium carbonate, and water. Carbon tetrachloride was stripped off, and the residue was distilled through a 10-cm. Vigreux column to give 7.9 g. (79% yield) of ketone whose infrared absorption spectrum was that of 2-methyl-4-*t*-butylacetophenone.

Similar treatment of 2-methyl-5-*t*-butylacetophenone (99.4–99.8 mole % pure) and 3-methyl-5-*t*-butylacetophenone (99.0–99.5 mole % pure) showed that these ketones also were not isomerized under the conditions employed, which were the conditions used in the acetylation of *p-t*-butyltoluene.

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(14) Baur-Thurgau, *Ber.*, **31**, 1345 (1898).

[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY]

Constant *Ortho* Effect with an Interacting Substituent

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Infrared spectra of a number of substituted anthranilic acids were determined in chloroform and in potassium bromide disks. The extensive hydrogen bonding present in chloroform solution appears to involve both carboxyl and amino groups, but the infrared results suggest that in the solid state hydrogen bonding is confined to the carboxyl groups. No evidence exists for the presence of zwitter ion structures in these compounds. Carbonyl frequencies are linearly related to the σ values of the substituent groups. In spite of the broadening of the carbonyl bands produced by hydrogen bonding, the relation with σ values is readily appreciated from the solution data, but is less apparent from data obtained with solids. Comparison of the spectra of substituted benzoic and anthranilic acids shows that the amino group exerts a constant influence on the carbonyl stretching frequency.

A second substituent R in a benzene ring produces an effect on the reactivity and other properties of the first substituent *Y* which is dependent on the nature and position of R. If the latter group is present in the *meta* or *para* position with respect to *Y*, its effect on *Y* is usually related to the σ value of the R group.[2,3] In multiple substitution, σ constants of the substituents are additive, since in any reaction series in which only the original substituent is modified, the entropy changes are presumably constant. Although σ values cannot be allocated to substituents in the *ortho* position to *Y*, this essential additivity property is likely to be preserved. Thus the presence of a further substituent *X* in the *ortho* position to group *Y* should produce a constant effect on the properties and reactivity of group *Y* in a series of substituted compounds.[3,4]

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(1) British Empire Cancer Campaign Research Fellow.

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 188.

(3) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

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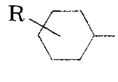
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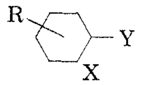
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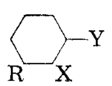
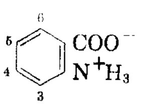

III

Differences in some measurable reactivity, or other property, of group *Y* in the corresponding structures I and II should therefore be independent of the particular R group selected. In structure III mutual interactions of groups R and *X* might be expected to complicate this relationship and possibly variable interactions, such as hydrogen bonding, occurring between groups *X* and *Y* could also give rise to discrepancies. It should clearly be possible to interchange the roles of substituents *X* and *Y* so that for suitable reactivities and properties of group *X*, the presence of substituent *Y* will exert a constant effect.

Substituted anthranilic acids were selected for study because of the interesting structural and hydrogen bonding possibilities of these compounds and in order to examine the constancy of the *ortho* effect in a series of compounds in which strong interaction is to be expected between the adjacent *X* and *Y* groups.

The structural possibilities for anthranilic acid and its derivatives include the zwitter ion IV and related forms produced by dipolar association, an intramolecularly bonded form V, and a variety of intermolecularly bonded structures of which VI possesses the associated carboxylic acid group and others possess the amino group of one molecule linked to the carboxyl group of an adjacent molecule.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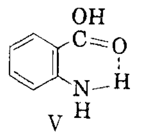
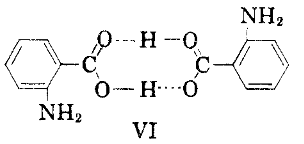

V


VI

In addition to these, anthranilic acid exists in various polymorphic forms which might be related to the possible existence of different types of polymeric association.[5] Previous investigations have not fully elucidated the structural problems outlined above. X-ray studies[5,6,7,8] have given information on the crystal habit of anthranilic acid in its different modifications, but have shed little light on its molecular structure. Data on solubilities, molecular volumes, dissociation constants, heats of neutralization, dielectric constants and chemical reactivities[9,10] indicate that the nonpolar form is the main structure of anthranilic acid, even in aqueous solution, while the polar forms may be of greater significance in *m*- and *p*-aminobenzoic acids. This is also supported by the infrared spectrum of anthranilic acid. Three crystalline forms of anthranilic acid have been examined in Nujol mulls by infrared spectroscopy[5] and, although the main features were reproduced, sufficient minor variations occurred to permit Ebert and Gottlieb[5] to suggest the use of infrared spectroscopy as a tool in the study of polymorphism. Studies of the carbonyl stretching frequencies of methyl anthranilate and methyl salicylate have shown that intramolecular hydrogen bonding is present in these compounds.[11]

RESULTS AND DISCUSSION

The presence of two NH_2 and one CO stretching frequencies in their normal positions in solid anthranilic acids, together with the absence of any bands that can be definitely attributed to zwitter ion forms, indicate that further consideration of this type of structure is unnecessary. The very broad band between 3500 and 2800 cm.$^{-1}$ which appears in the spectrum of a few substituted anthranilic acids, examined in this region in chloroform solution, suggests the occurrence of both intra- and intermolecular hydrogen bonding. The infrared spectra of substituted anthranilic acids in potassium bromide disks possess the asymmetric and symmetric NH_2 bands of medium intensity near 3500 and 3400 cm.$^{-1}$, respectively. A broad band of about the same intensity is present in the 3100 to 2800 cm.$^{-1}$ region and a broad band of somewhat lower intensity, which forms a shoulder on the previous band and itself possesses several indistinct submaxima, is present between 2800 and 2500 cm.$^{-1}$ in all the compounds. This broad absorption is identical with that of benzoic acid and is in the frequency range characteristic of the associated carboxylic acid group. Absence of any indication of free hydroxyl absorption at 3650 cm.$^{-1}$ and of any maximum near 3300 to 3200 cm.$^{-1}$, which is to be associated with the NH . . . OC linkage, confirms the suggestion that in the solid state, association occurs through the carboxyl groups. Slight broadening of the carboxyl absorption at certain other wave numbers also supports structure VI as representing the association of anthranilic acid molecules in the solid state. Two compounds that exhibit variations from this scheme are 3- and 6-nitroanthranilic acids. The differences that appear in lower frequency absorptions of these acids suggest that the 3-nitro compound possesses intramolecular NO . . . HN bonding in addition to the intermolecular

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(5) A. A. Ebert and H. B. Gottlieb, *J. Am. Chem. Soc.*, **74**, 2806 (1952).

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(9) P. Spinoglio and F. Brunello, *Gazz. chim. ital.*, **67**, 256 (1937).

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(11) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

bonding already postulated. Considerable broadening of the NH_2 frequencies, so that they coalesce to give a single band, with the 6-nitro compound implies that the intermolecular bonding might involve the $NO_2 \ldots H_2N$ linkage as well as the associated carboxylic acid group.

Table I shows that a correlation exists between both the asymmetric and symmetric NH_2 stretching vibrations and the σ constants[2,3] of the substituent groups with reference to their positions relative to the NH_2 group. These values, being with reference to position 2 in the ring, are given the symbol σ_2. A similar correlation was observed by Flett[12] with substituted anilines in carbon tetrachloride. The data for the 6-nitro compound clearly cannot be considered for correlation purposes and methoxy compounds frequently possess anomalous behavior.[3] Equations of the regression lines for the remaining relevant data in Table I are $\nu = 3485 + 74.9\sigma_2$ and $\nu' = 3377 + 64.1\sigma_2$. Correlation coefficients[3] for the asymmetric and symmetric NH_2 frequencies are 0.817 and 0.770, respectively.

TABLE I

HAMMETT'S σ CONSTANTS AND ASYMMETRIC (ν) AND SYMMETRIC (ν') NH_2 FREQUENCIES[a] OF SUBSTITUTED ANTHRANILIC ACIDS

Substituent	σ_2	ν	ν'
5-Me	−0.170	3450	3335
4-Me	−0.069	3500	3395
None	0	3500	3395
4-MeO	0.115	3453	3355
5-Cl	0.227	3500	3385
4-I	0.352	3505	3405
4-Cl	0.373	3510	3400
4-Br	0.391	3517	3400
4-NO_2	0.710	3535	3415
6-NO_2	0.710	3460–3360[b]	
3-I	. . .	3435	3325
3-Cl	. . .	3490	3375
3-NO_2	. . .	3480	3355

[a] All bands of medium intensity relative to the carbonyl absorption. [b] Broad band.

All the anthranilic acids show intense absorption in the 1670 cm.$^{-1}$ region, produced by the stretching vibrations of the C═O group. In all cases only one maximum is obtained but frequently, both in chloroform and as disks, this is broadened over about 6 wave numbers owing to hydrogen bonding.

Where the maxima are not absolutely sharp the central frequency is quoted. It can be seen from Table II that the carbonyl frequencies, both in chloroform and in disks, can be correlated with the σ values of the substituents considered in relation to the carbonyl group (σ_1). This correlation is better with solutions than with disks, but in view of the extensive hydrogen bonding that occurs it can be considered satisfactory even with the solids. Although the anthranilic acid used was crystallized from water and should therefore be the normal form, the results obtained using potassium bromide disks agree better with results given by Flett[13] for the high temperature form and therefore it seems likely that a transition occurred in the preparation of the disks.

In view of the uncertainty attached to the σ value of the *p*-nitro group,[3] 4-nitroanthranilic acid has been omitted from a quantitative consideration of the correlations. Regression lines for the data presented in Table II obey the equation $\nu_c = 1674 + 11.5\sigma_1$ and $\nu_d = 1666 + 11.9\sigma_1$ and the correlation coefficients for solutions and disks are 0.887 and 0.642, respectively.

TABLE II

σ VALUES AND CARBONYL FREQUENCIES OF ANTHRANILIC ACIDS

Substituent	σ_1	$\nu_c{}^{a}$	$\nu_d{}^{b}$
4-MeO	−0.268	[d]	1658
4-Me	−0.170	1673	1660
5-Me	−0.069	1674	1675
None	0	1673	1668
4-F	0.062	1675	[d]
4-Cl	0.227	1676	1667
4-Br	0.232	[d]	1667
4-I	0.276	[d]	1672
3-F	0.337	1678	[d]
5-F	0.337	1680	[d]
3-I	0.352	1676	1669
3-Cl	0.373	1680	1668
5-Cl	0.373	1679	1668
3-Br	0.391	1678	[d]
3-CF_3	0.415[c]	1680	[d]
3-NO_2	0.710	1683	1675
4-NO_2	1.27	1686	1675
6-NO_2	. . .	[d]	1672

[a] CO frequencies in chloroform. [b] CO frequencies in disks. [c] H. H. Jaffé, *Chem. Revs.*, **53**, 222 (1953). [d] Not measured.

An examination of the vibrational spectra of 60 assorted carboxylic acids enabled Flett[13] to suggest a range of frequencies characteristic of the carboxyl group. All these bands occur in a well defined form in the acids we have investigated. Frequencies near 2700 cm.$^{-1}$ and 1670 cm.$^{-1}$ have already been considered and the remaining carboxyl bands are collected in Table III. The band near 1430 cm.$^{-1}$ is probably a C—O— stretching vibration. In this series the bands near 1430 cm.$^{-1}$ and 1250 cm.$^{-1}$ are well defined, the latter in particular being intense and usually possessing a slightly broad maximum. These frequencies appear to increase with the σ value of the substituent. The absorption near 900 cm.$^{-1}$ is of a more variable character.

The relation between the carbonyl frequencies of substituted anthranilic acids in chloroform and the σ_1 values is approximately linear, the slope being similar to that found in both benzoic acid monomers

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(12) M. St. C. Flett, *Trans. Faraday Soc.*, **44**, 767 (1948).

(13) M. St. C. Flett, *J. Chem. Soc.*, 962 (1951).

TABLE III

LOWER FREQUENCY COOH BANDS[a]

Sub-stituent			
4-MeO	1428 m	1248 s	918 vw
4-Me	1430 m	1248 s	933 w
5-Me	1430 m	1250 s	918 w 904 w
None	1428 s	1253 s	924 s
4-Cl	1432 s	1253 s	921 s 900 m
4-Br	1435 s	1252 s	903 s
4-I	1433 m	1252 s	894 m
3-I	1447 m 1420 m	1266 m 1248 s	900 w
3-Cl	1425 s	1274 s 1258 s	922 vw 896 w
5-Cl	1430 m	1245 s	[b]
3-NO_2	1442 m	1258 s	884 w
4-NO_2	1433 m	1255 s	885 w
6-NO_2	1460 m 1428 w	1274 s 1217 s	888 vw

[a] Substituted anthranilic acids in potassium bromide disks. [b] Not measured.

and dimers.[12,14,15] This demonstrates the constancy of the effect of the amino group on the carbonyl group. Specific illustration of this feature is given in Table IV. A similar comparison of carbonyl frequencies for the solids, is given in Table V. The discrepancy in the case of 6-nitroanthranilic acid is not unexpected as the nitro group is adjacent to the carboxyl group. Constancy in the effect of an *ortho* substituent on carbonyl frequencies is also implicit in previous infrared data on substituted isatins.[16]

TABLE IV

EFFECT OF NH_2 GROUP ON CO FREQUENCIES OF ANTHRANILIC ACIDS IN SOLUTION

Sub-stituent[a]	ν^b	$\nu_0{}^c$	$\nu - \nu_0$
4-Me	1673	1739	−66
None	1673	1743	−70
4-Cl	1676	1746	−70
3-Cl	1680	1746	−66
5-Cl	1679	1746	−67
3-NO_2	1683	1750	−67

[a] Numbering for substituents refers to anthranilic acid. [b] Frequencies for substituted anthranilic acids in chloroform. [c] Figures given by Flett[12] for the corresponding benzoic acid monomers in carbon tetrachloride.

TABLE V

EFFECT OF NH_2 GROUP ON CO FREQUENCIES OF SOLID ANTHRANILIC ACIDS

Sub-stituent[a]	ν^b	$\nu_0{}^c$	$\nu - \nu_0$
None	1668	1685	−17
4-Cl	1667	1685	−18
3-NO_2	1675	1690	−15
4-NO_2	1675	1690	−15
6-NO_2	1672	1700	−28

[a] Numbering for substituents refers to anthranilic acid. [b] Frequencies for anthranilic acids in potassium bromide disks. [c] Figures given by Flett[13] for the corresponding benzoic acid dimers in Nujol mulls.

Interesting information was expected on the effect of the carboxyl group on the two amino stretching frequencies but, owing to the broad character of the NH_2 absorptions in aromatic amines in the solid state, data for comparison purposes could not be obtained.

EXPERIMENTAL

Spectra. Infrared data were obtained with a Perkin-Elmer 21 double-beam recording spectrometer fitted with a rock-salt prism.

Compounds. Substituted anthranilic acids were prepared by alkaline peroxide oxidation of the corresponding isatins using a method previously described.[17,18]

3-Trifluoromethylanthranilic acid was obtained as white needles from aqueous ethanol, m.p. 159°.

Anal. Calc'd for $C_8H_6F_3NO_2$: C, 46.8; H, 2.9. Found: C, 46.6; H, 3.0.

3-Fluoroanthranilic acid was obtained as white plates from aqueous ethanol and had m.p. 183°.

Anal. Calc'd for $C_7H_6FNO_2$: C, 54.2; H, 3.9. Found: C, 54.0; H, 3.8.

Acknowledgment. The authors thank Mr. A. Madle for his assistance with the measurements.

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