76. *The Associating Effect of the Hydrogen Atom. Part II. Substituted Anilides and Related Substances.*

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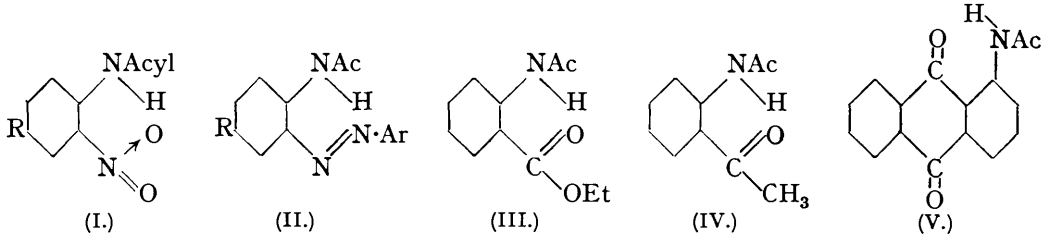
The molecular condition of 30 acylamino-compounds has been deduced from cryoscopic and wet melting-point measurements. Although certain *o*-substituted acylamines give indication of chelate ring formation between the two neighbouring

groups, substitution of a group in the second ortho-position prevents chelation. This fact is interpreted as evidence of restricted rotation about the nitrogen-nuclear single bond in 2 : 6-disubstituted acylamines.

THE suggestion was made in Part I (J., 1937, 1114) that the suppression of the tendency to associate in acetanilide by the substitution of certain *o*-groups may be due to chelate ring formation between such groups and the acetamido-group, involving the amide hydrogen atom. Reference to the cryoscopic measurements of von Auwers and his co-workers (*loc. cit.*) will show that the *o*-substituents most effective in this respect are hydrogen-acceptor groups such as $-NO_2$ and $-CHO$, and that other groups (*e.g.*, CH_3, Cl, OCH_3) have a relatively small effect on the association factor. It would appear, therefore, that the engagement of the amide hydrogen atom by co-ordination with a suitable *o*-substituent will prevent the intermolecular sharing of this hydrogen, which is the cause of molecular association in the amides. A similar interpretation of von Auwers's results was published by Lassettre (*Chem. Reviews*, 1937, **20**, 259) almost simultaneously with Part I of this series.

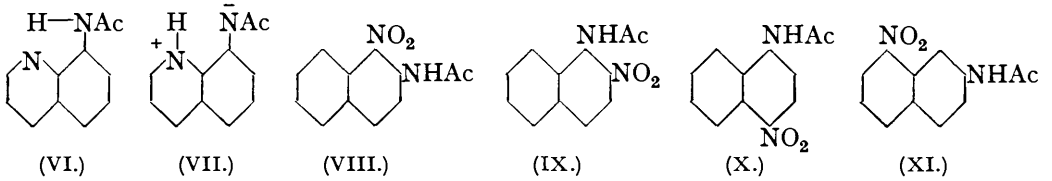
An examination has now been made of a sufficient number of substituted anilides to confirm this suggestion. In a series of nitro-acylanilines, only those derived from *o*-nitroaniline (I; R = H, Acyl = acetyl, benzoyl, *p*-toluenesulphonyl) were unassociated, the *m*- and *p*-isomers exhibiting considerable association with increasing concentration



(Fig. 1). Similar tendencies were observed in *o*-acetamidoazo-compounds (II; Fig. 2), ethyl *o*-acetamidobenzoate (III; Fig. 3), *o*-acetamidoacetophenone (IV; Fig. 3), and 1-acetamidoanthraquinone (V).

The factors of association of these compounds were calculated from cryoscopic measurements in naphthalene, and it is significant that the *o*-compounds are almost invariably more soluble in this solvent than the *m*- and *p*-isomers. Evidence confirming a chelate structure in the *o*-compounds was also provided in the wet melting-point data. This device has been developed by Baker (J., 1934, 1687, and subsequent papers), who has interpreted the results as indicating that the isomer possessing a chelate structure shows the least depression of melting point in the presence of water. Although the limitations of this test are fully realised, the results are sufficiently parallel to those obtained cryoscopically to justify their use as confirmatory evidence.

The case of 8-acetamidoquinoline (VI) differs somewhat from those just considered in having as the hydrogen acceptor the quinoline nitrogen atom. This can accept hydrogen only by becoming an ammonium ion, and since the substance is undoubtedly chelated



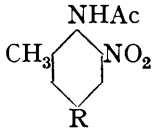
(Fig. 4), it probably exists as a resonance hybrid of (VI) and the zwitterion (VII). In this respect 8-acetamido- resembles 8-hydroxy-quinoline. As was anticipated, 6-acetamido-quinoline is associated and non-chelate (Fig. 4).

In the following comparison of four isomeric nitroacetnaphthalides it was observed that

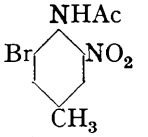
1-nitro-2-acetnaphthalide (VIII) has properties consistent with a chelate structure; it is not markedly associated, is more soluble in naphthalene, has a lower m. p., and in the

	M. p.	Wet m. p.	Δ.	
1-Nitro-2-acetnaphthalide (VIII)	123—124°	110°	13—14°	Not associated.
2-Nitro-1-acetnaphthalide (IX)	199	166	33	Associated.
4-Nitro-1-acetnaphthalide (X)	190	144	46	Associated.
8-Nitro-2-acetnaphthalide (XI)	195	154	41	Associated.

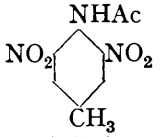
presence of water shows the smallest m. p. depression of the four isomers examined. On the other hand, 2-nitro-1-acetnaphthalide (IX) has the reverse of these properties, and is much more closely comparable with the isomers (X) and (XI), in which chelation is structurally impossible. It appeared likely that the absence of a co-ordinated structure in 2-nitro-1-acetnaphthalide (IX) might be due to steric interference between the large acetyl group and the *peri*-CH group of the naphthalene nucleus, thus preventing the amide hyrogen atom from approaching sufficiently near to the nitro-group to achieve chelation. This view has been confirmed by the examination of a number of 6-substituted



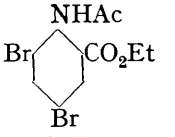
(XII.)



(XIII.)



(XIV.)



(XV.)

o-nitroacetanilides, in which similar steric effects might be expected. The substitution of methyl (XII, R = H or CH_3), bromine (XIII), or nitroxyl (XIV) in the 6-position in *o*-nitroacetanilide has the same effect as the naphthalene nucleus in (IX), causing the resulting compounds to show no chelate properties, and to be associated in naphthalene solution. In a similar way the anomalous non-chelate properties of 2 : 3-dinitrophenol (Sidgwick and Aldous, J., 1921, **119**, 1008) and ethyl quinol-2 : 3-dicarboxylate (Baker and Carruthers, J., 1937, 479) are evidently due to steric interference of a type similar to that postulated above.

An interesting consequence of the chelate structure ascribed to 3-nitroaceto-*p*-toluidide (I, R = CH_3, Acyl = acetyl) is that it was found impossible to bring about direct bromination to 3-bromo-5-nitroaceto-*p*-toluidide (XIII). This is no doubt to be attributed to the orientation of the acetyl group, owing to chelation in (I; R = CH_3, Acyl = acetyl), in such a manner as to cause protection of the 3-position, thus hindering the approach of the substituting bromine. The bromination was eventually effected through the free amine, in which no such hindrance is possible, followed by acetylation.

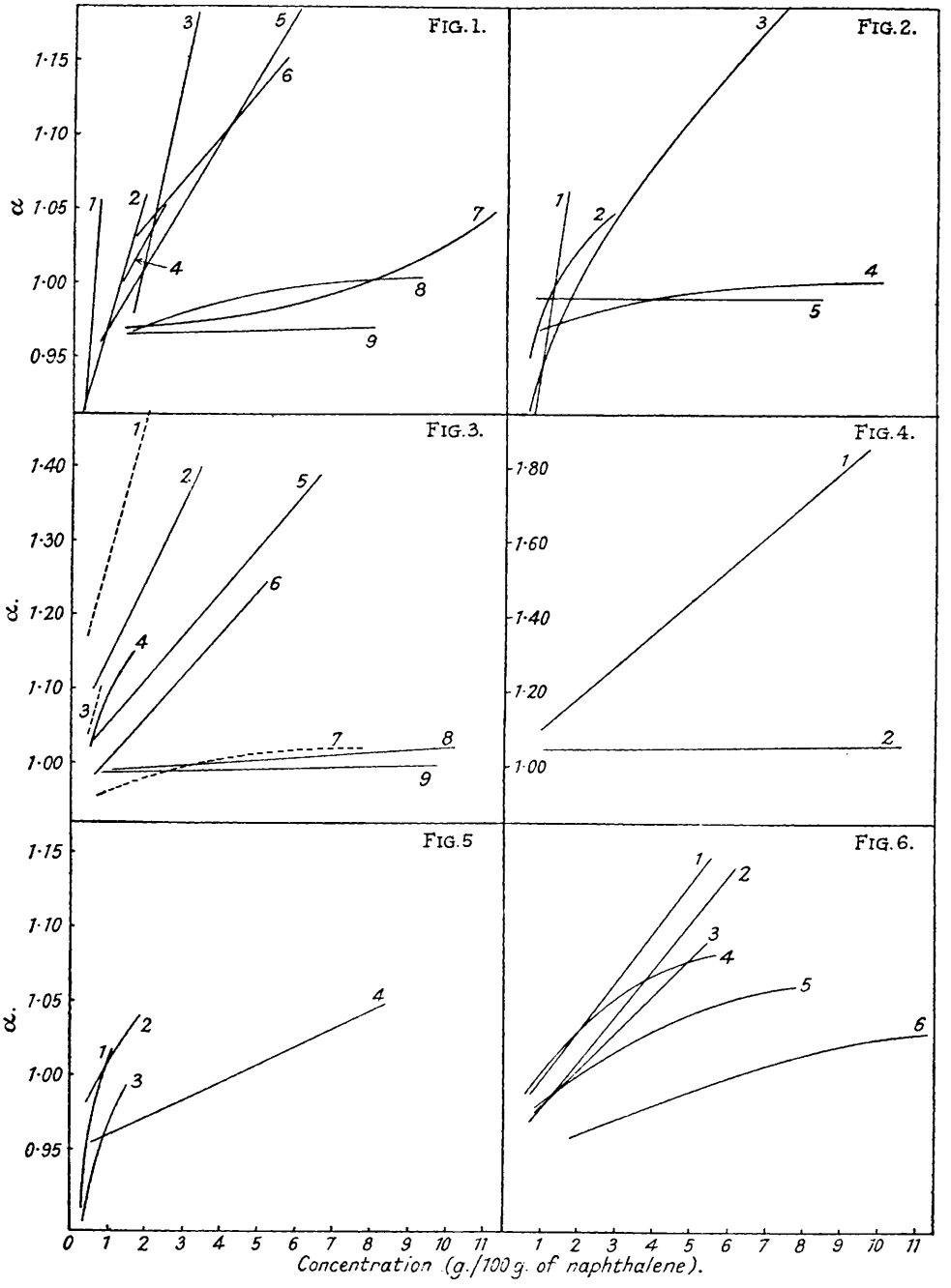
The effect of the 6-bromine atom in *ethyl 3 : 5-dibromo-2-acetamidobenzoate* (XV) is not so marked as in the case of the nitro-compounds (IX, XII, XIII, and XIV), the association–concentration curve lying midway between those typical of associated and non-associated substances (Fig. 6). This is presumably due to the stronger tendency of the carbethoxy-group, as compared with the nitro-group, to co-ordinate with hydrogen, and this conclusion is in harmony with the order of the "normalising" effect of *o*-substituents deduced by von Auwers and Pelzer (*Z. physikal. Chem.*, 1897, **23**, 449). The wet m. p. data for this substance (below), however, point to a non-chelate structure, thus

	M. p.	Wet m. p.	Δ.
Ethyl 3 : 5-dibromo-2-acetamidobenzoate (XV)	137°	117°	20°
Ethyl *o*-acetamidobenzoate (III)	66	61	5
Ethyl m-*acetamidobenzoate*	84	64	20
Ethyl *p*-acetamidobenzoate	103—104	71	32—33

confirming a steric effect. It should be pointed out that the steric effect in any of the substances quoted is not assumed to prevent chelation entirely; in fact, association of such compounds is generally less marked than for typically associated compounds, and at the same time the solubility in hydrocarbon solvents is generally greater.

An inevitable consequence of the non-coplanar distribution of the acetamido-group in compounds of the 2 : 6-disubstituted acetanilide type (XII—XV) is that these substances

acquire molecular asymmetry. The failure to resolve such compounds (Tuan, Hsü, and Hsü, *J. Chinese Chem. Soc.*, 1936, **4**, 131) is probably due to rapid racemisation of the enantiomorphs; but whereas the effect of racemisation on optical rotatory power is to



diminish or destroy it, its effect on the association factor is negligible. This view has been fully discussed elsewhere (*Nature*, 1937, **140**, 896).

In the following tables and curves, the association factors have been calculated according to the ideal-solution laws, and are thus to be regarded only as a semi-quantitative

indication of association. Conclusions concerning association are based, not on the absolute values of the association factor (which may have no real significance), but rather on the slope of the association–concentration curves; molecular association in a substance is

FIG. 1.

1 = *p*-Nitroacetanilide.
2 = *p*-Nitrobenzanilide.
3 = *m*-Nitroacetanilide.
4 = *p*′-Toluenesulphon-*p*-nitroanilide.
5 = *m*-Nitrobenzanilide.
6 = *p*′-Toluenesulphon-*m*-nitroanilide.
7 = *o*-Nitroacetanilide (I; R = H, Acyl = COMe).
8 = *p*′-Toluenesulphon-*o*-nitroanilide (I; R = H, Acyl = $SO_2C_7H_7$).
9 = *o*-Nitrobenzanilide (I; R = H, Acyl = COPh).

FIG. 2.

1 = 1-Benzeneazo-4-acetnaphthalide.
2 = 4-Acetamido-3 : 2′-dimethylazobenzene.
3 = *p*-Acetamidoazobenzene.
4 = 1-Benzeneazo-2-acetnaphthalide.
5 = 2-Acetamido-5 : 4′-dimethylazobenzene (II; R = Me, Ar = *p*-tolyl).

FIG. 3.

1 and 5 = Ethyl-*m*-acetamidobenzoate.
2 = *m*-Acetamidoacetophenone.
3 and 6 = Ethyl *p*-acetamidobenzoate.
4 = *p*-Acetamidoacetophenone.
7 and 9 = Ethyl *o*-acetamidobenzoate (III).
8 = *o*-Acetamidoacetophenone (IV).

FIG. 4.

1 = 6-Acetamidoquinoline.
2 = 8-Acetamidoquinoline (VI).

FIG. 5.

1 = 8-Nitro-2-acetnaphthalide (XI).
2 = 4-Nitro-1-acetnaphthalide (X).
3 = 2-Nitro-1-acetnaphthalide (IX).
4 = 1-Nitro-2-acetnaphthalide (VIII).

FIG. 6.

1 = 3-Nitro-*o*-acetotoluidide (XII; R = H).
2 = 5-Nitro-4-aceto-*m*-xylidide (XII; R = Me).
3 = 3-Nitro-5-bromo-*p*-acetotoluidide (XIII).
4 = 3 : 5-Dinitro-*p*-acetotoluidide (XIV).
5 = Ethyl 3 : 5-dibromo-2-acetamidobenzoate (XV).
6 = 3-Nitro-*p*-acetotoluidide (I; R = Me, Acyl = COMe).

inferred from a steep curve, and absence of association from a flat or gently sloped curve. In the tables, concentrations are given as g./100 g. of naphthalene, M is the apparent molecular weight, α is the association factor, and Δ is the depression of melting point in the presence of water. Figures in parentheses indicate the normal molecular weight; those in italics are calculated from the measurements of von Auwers and Pelzer (*loc. cit.*). The broken lines in Fig. 3 are for solutions in benzene.

	Concn.	*M*.	α.	M. p.	Wet m. p.	Δ.
Acyl derivatives of the nitroanilines (Fig. 1).						
o-Nitroacetanilide (180)	*1·9*	*176*	*0·97*	92°	82°	10°
(I; R = H, Acyl = $COCH_3$)	*6·8*	*179*	*0·99*			
	11·8	*192*	*1·07*			
m-Nitroacetanilide	*1·7*	*177*	*0·98*	155	120	35
	3·2	*213*	*1·18*			
p-Nitroacetanilide	*0·32*	*164*	*0·91*	210	159	51
	0·57	*189*	*1·05*			
	0·76	*190*	*1·06*			
o-Nitrobenzanilide (242)	0·52	232·7	0·96	93	85	8
(I; R = H, Acyl = COPh)	1·48	234·4	0·97			
	2·93	232·1	0·96			
	5·10	234·7	0·97			
	7·92	234·1	0·97			
m-Nitrobenzanilide	0·82	231·3	0·96	154	133	21
	1·98	246·6	1·02			
	3·19	257·7	1·065			
	4·44	268·5	1·11			
	6·19	289·9	1·20			
p-Nitrobenzanilide	0·19	218·8	0·90	196	167	29
	0·49	225·6	0·93			
	1·14	237·8	0·98			
	1·95 *	257·1	1·06			
p′-Toluenesulphon-*o*-nitroanilide (292)	1·56	283·0	0·97	115	109	6
I; R = H, Acyl = $SO_2C_7H_7$)	2·74	282·6	0·97			
	5·32	291·6	1·00			
	8·75	292·0	1·00			

* Solute separates at higher concentrations.

	Concn.	*M.*	*a.*	M. p.	Wet m. p.	Δ.
p'-Toluenesulphon-*m*-nitroanilide	0·72	293·7	1·01	138°	117°	21°
	1·69	301·3	1·03			
	4·31	323·6	1·11			
	5·58	336·5	1·15			
p'-Toluenesulphon-*p*-nitroanilide	1·22	293·3	1·00	189	159	30
	2·60 *	309·1	1·06			
p-Acetamidoazobenzene (239)	0·78	217·3	0·91	144—145	128	16—17
	2·13	243·3	1·02			
	3·47	255·7	1·07			
	4·97	267·8	1·12			
	7·36	283·2	1·185			
2-Acetamido-5 : 4'-dimethylazobenzene (267)	0·87	264·3	0·99	156—157	142—143	14
	1·96	262·4	0·98			
(II; R = Me, Ar = *p*-tolyl)	3·55	265·3	0·99			
	5·76	264·3	0·99			
	8·43	264·2	0·99			
4-Acetamido-3 : 2'-dimethylazobenzene	0·675	254·4	0·95	185	161	24
	1·665	271·6	1·02			
	2·97 *	279·7	1·05			
1-Benzeneazo-2-acetnaphthalide (289)	0·97	279·4	0·97	154	138	16
	2·48	282·4	0·98			
	4·69	284·8	0·99			
	7·05	288·6	1·00			
	9·93	289·0	1·00			
1-Benzeneazo-4-acetnaphthalide	0·63	259·7	0·90	232—233	187—188	45
	1·31	286·6	0·99			
	1·67 *	307·1	1·06			
Acetamido-benzoates, -acetophenones, and -anthraquinones (Fig. 3.).						
Ethyl *o*-acetamidobenzoate (207) (III)	0·86	204·6	0·99	66	61	5
	4·46	204·0	0·99			
	7·43	201·9	0·975			
	9·69	204·0	0·985			
(in benzene)	0·68	197·4	0·95			
	2·04	203·2	0·98			
	3·70	208·0	1·005			
	5·32	208·9	1·01			
	7·58	210·6	1·02			
Ethyl *m*-acetamidobenzoate	0·71	213·6	1·03	84	64	20
	2·09	232·1	1·12			
	4·35	258·7	1·25			
	6·72	288·3	1·39			
(in benzene)	0·39	242·4	1·17			
	0·91	257·6	1·24			
	1·38	277·7	1·34			
	2·09	316·1	1·53			
Ethyl *p*-acetamidobenzoate	0·64	205·5	0·99	103—104	71	32—33
	2·04	220·0	1·06			
	3·71	243·7	1·18			
	5·22	257·3	1·24			
(in benzene)	0·46	214·5	1·04			
	0·825 *	228·2	1·10			
o-Acetamidoacetophenone (177) (IV)	1·16	174·5	0·99	78	63	15
	3·665	174·4	0·985			
	6·38	177·2	1·00			
	10·27	181·6	1·03			
m-Acetamidoacetophenone	0·68	195·3	1·10	126	86	40
	1·42	208·3	1·18			
	2·40	231·8	1·31			
	3·60	246·7	1·39			
p-Acetamidoacetophenone	0·585	180·2	1·02	167	117	50
	1·09	196·0	1·11			
	1·695 *	203·0	1·15			
1-Acetamidoanthraquinone (265) (V)	0·45	260·8	0·98	215	186	29
	1·01	262·1	0·99			
	1·65	264·5	1·00			
	2·75	247·1	0·93			
	4·63	251·4	0·95			
2-Acetamidoanthraquinone	0·30 *	272·2	1·03	263	201	62

* Solute separates at higher concentrations.

	Concn.	*M.*	α.	M. p.	Wet m. p.	Δ.
Acetamidoquinolines (Fig. 4).						
6-Acetamidoquinoline (186)	1·035	203·5	1·09	138—139°	71°	67—68°
	2·71	228·1	1·23			
	6·19	286·1	1·54			
	9·70	344·6	1·85			
8-Acetamidoquinoline (VI)	1·02	193·7	1·04	103	82	21
	3·63	193·6	1·04			
	7·73	192·9	1·04			
	10·61	196·0	1·05			
Nitroacetnaphthalides (Fig. 5).						
1-Nitro-2-acetnaphthalide (230) (VIII)	0·70	219·8	0·96	123—124	110	13—14
	1·49	221·5	0·96			
	2·92	223·6	0·97			
	4·07	229·5	1·00			
	5·79	233·6	1·02			
	8·37	240·5	1·05			
8-Nitro-2-acetnaphthalide (XI)	0·355	209·5	0·91	195	154	41
	0·75	229·4	1·00			
	1·29 *	235·3	1·02			
2-Nitro-1-acetnaphthalide (IX)	0·31	206·6	0·90	199	166	33
	0·605	216·4	0·94			
	1·36 *	226·9	0·99			
4-Nitro-1-acetnaphthalide (X)	0·44	225·2	0·98	190	144	46
	1·21	234·8	1·02			
	1·86 *	238·7	1·04			
oo′-*Disubstituted derivatives of acetanilide* (Fig. 6).						
3-Nitro-*p*-acetotoluidide (194)	*1·94*	*186*	*0·96*	91	79	12
(I; R = Me, Acyl = COMe)	*5·44*	*193*	*0·995*			
	8·88	*198*	*1·02*			
	11·23	*200*	*1·03*			
3-Nitro-*o*-acetotoluidide	0·83	191·7	0·99	158	121	37
(XII; R = H)	1·29	195·6	1·01			
	1·71	198·7	1·02			
	2·41	202·2	1·04			
	3·34	206·0	1·06			
	4·17	212·8	1·10			
	5·525	222·6	1·15			
5-Nitro-4-aceto-*m*-xylidide (208)	0·73	201·8	0·97	172—173	144	28—29
(XII; R = Me)	1·49	205·3	0·99			
	2·99	216·2	1·04			
	4·64	226·8	1·09			
	6·18	237·7	1·14			
3-Bromo-5-nitro-*p*-acetotoluidide (273)	1·025	267·9	0·98	210—211	165	45—46
(XIII)	2·13	275·2	1·01			
	3·88	286·6	1·05			
	5·38	297·7	1·09			
3 : 5-Dinitro-*p*-acetotoluidide (239)†	0·65	235·7	0·99	190·5	157	33·5
(XIV)	1·94	246·7	1·03			
	3·74	254·3	1·06			
	5·78	256·9	1·075			
Ethyl 3 : 5-dibromo-2-acetamido-	0·93	358·9	0·98	137	117	20
benzoate (365) (XV)	2·44	373·9	1·02			
	5·29	380·6	1·04			
	7·425	385·7	1·06			

* Solute separates at higher concentrations.

Experimental.

Molecular weights were measured cryoscopically in naphthalene; those of the ethyl acetamidobenzoates also in benzene. Wet m. p.'s were carried out in small sealed tubes of average length 1·5 cm. and average internal diameter 1·5 mm.; observations were carefully checked to eliminate the possibility of hydrolysis. Materials were prepared and purified by usual methods, and the m. p.'s of known compounds are reported only when they differ from those recorded in the literature. They are as follows: *p′*-toluenesulphon-*o*-nitroanilide, m. p. 115° (lit., 110°); *p*-acetamidoazobenzene, m. p. 144—145° (lit., 144—146°); ethyl *o*-acetamidobenzoate, m. p. 66° (lit., 61—62°, 64—65°); ethyl *p*-acetamidobenzoate, m. p. 103—104° (lit., 110°) (Found: N, 6·62. Calc.: N, 6·72%); *o*-acetamidoacetophenone, m. p. 78° (lit., 76°); ethyl 3 : 5-dibromo-*o*-aminobenzoate, m. p. 76° (lit., 74°).

The following new compounds were prepared in the course of the investigation. *Ethyl* m

acetamidobenzoate, prepared by acetylating the free amine, formed white needles from alcohol, m. p. 84° (Found : N, 6·64. $C_{11}H_{13}O_3N$ requires N, 6·76%). *Ethyl* **3** : **5**-*dibromo*-o-*acetamidobenzoate* was prepared by aspirating bromine vapour (2 mols.) through a solution of ethyl anthranilate (1 mol.) in glacial acetic acid, and acetylating the product (m. p. 76°) by Smith and Orton's method (J., 1908, **93**, 1249). It crystallised from aqueous alcohol in fine white needles, m. p. 137° (Found : N, 3·9. $C_{11}H_{11}O_3NBr_2$ requires N, 3·8%).

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