The Reaction of Phenyl Iodosoacetate with N-*Arylacetamides.*

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Acetanilide and certain derivatives, especially those containing negative substituents, do not react appreciably with phenyl iodosoacetate at room temperature, but those containing electron-releasing substituents in the *p*-position give high yields of *m*-acetoxy-derivatives. Quinonoid products are obtained from other *N*-arylacetamides. The mechanism of the acetoxylation is discussed.

IN the preceding paper it was shown that β-naphthylamine and phenyl iodosoacetate in acetic acid gave mainly 2-acetamido-1 : 4-naphthaquinone and a compound, $C_{22}H_{16}O_2N_2$, believed to be a β-naphthylanil of the quinone, probably by way of aceto-β-naphthalide which indeed with phenyl iodosoacetate in acetic acid produces the quinone in good yield, but not the supposed anil. Reaction also occurs in benzene but much more slowly (see the Table), and the yield of quinone is lower.

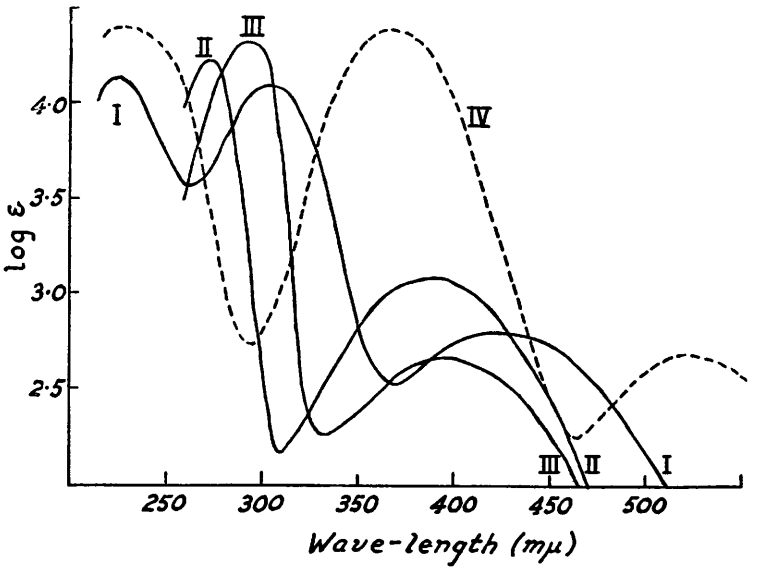
Although acetanilide and aceto-*m*-toluidide reacted slowly, and aceto-α-naphthalide rapidly, with phenyl iodosoacetate in acetic acid at room temperature, no identifiable products were obtained. The negatively substituted chloro- and nitro-acetanilides reacted negligibly slowly, but other *N*-arylacetamides readily. The Table shows the uptakes of reagent, determined by Pausacker's method (*J.*, 1953, 1989), which are some measure of the relative speeds of reaction; comparative results for benzene solution for some of the more reactive compounds are also given. No absolute significance is attached to the uptakes which increase slowly for several days.

Acetyl derivative of	$PhI(OAc)_2$ consumed (mol.) In AcOH 24 hr.	In AcOH 4 days	In C_6H_6 24 hr.	In C_6H_6 4 days
Aniline	0·0	0·2	—	—
o-Toluidine	1·4	1·9	0·0	0·0
m- ,,	0·0	0·3	—	—
p- ,,	1·2	1·6	0·3	0·5
Mesidine	2·4	2·7	—	—
o-Anisidine	1·9	2·4	—	—
p- ,,	2·0	2·5	0·1	0·2
p-Phenetidine	1·9	2·5	—	—
α-Naphthylamine	2·2	2·6	—	—
β- ,,	2·2	2·3	0·5	1·3

Aceto-*p*-toluidide, aceto-*p*-anisidide, and phenacetin underwent acetoxylation in a position *meta* to the acetamido-group, yields being good. The orientation was unexpected, and the product from aceto-*p*-toluidide was rigorously identified to prove it. Sandin and McCormack (*J. Amer. Chem. Soc.*, 1945, **67**, 2051) found phenyl iodosoacetate to be a methylating agent toward trinitrotoluene, as is also lead tetra-acetate (Fieser, Clapp, and Daudt, *ibid.*, 1942, **64**, 2052) which, at lower temperatures, acetoxylates reactive aromatic hydrocarbons (Fieser *et al.*, *ibid.*, 1938, **60**, 2542, 1893; 1940, **62**, 432). No record of Sandin's proposed investigation of phenyl iodosoacetate as an acetoxylating agent (*Chem.*

Reviews, 1943, **32**, 260) has been found, and the present work seems to be the first report of its efficacy in this respect toward the aromatic nucleus, although Criegee and Beucker (*Annalen*, 1939, **541**, 218) found that it converted unsaturated compounds into glycol diacetates.

Traces of yellow products were obtained in the reactions with aceto-*p*-toluidide and phenacetin, and the method of preparation and analyses suggest that these are 2-acetamido-5-methyl- and -5-ethoxy-*p*-benzoquinone, respectively. In confirmation, the ultra-violet absorption spectra (see Figure) resemble closely that of 2 : 5-bisdimethylamino-*p*-benzoquinone (Braude, *J.*, 1945, 490) displaced somewhat to shorter wave-lengths. Aceto-*o*-anisidide gave a moderate yield of an orange compound, $C_{11}H_{13}O_4N$ (which, for the above reasons, is probably 2-acetamido-3-methoxy-*p*-benzoquinone), and a colourless substance which gave analyses corresponding to those of an acetoxy-derivative of aceto-*o*-anisidide



I, 2-*Acetamido*-3-*methoxy*-p-*benzoquinone*.
II, 2-*Acetamido*-5-*methyl*-p-*benzoquinone*.
III, 2-*Acetamido*-5-*ethoxy*-p-*benzoquinone*.
IV, 2 : 5-*Bisdimethylamino*-p-*benzoquinone* (*redrawn from Braude*, loc. cit.).
Curve I determined in 95% EtOH, *the others in* $CHCl_3$.

but appeared to give a mixture on hydrolysis and subsequent methylation. By contrast, aceto-*o*-toluidide yielded no acetoxylation product, and the acetamido-group was not present in the quinonoid product, toluquinone.

Although the products from the reaction in benzene were examined only with aceto-β-naphthalide, the much greater rates of reaction and especially the formation of high yields of acetoxylation products from appropriate compounds in the polar solvent, acetic acid, may indicate that acetoxylation proceeds by an ionic rather than by a radical mechanism such as that postulated by Pausacker (*J.*, 1953, 107) for the conversion of amines into azo-compounds. In any case the initial stages cannot generally involve the acetamido-group for, if this group were attacked homolytically, nucleophilically, or electrophilically, the necessary reactivity for acetoxylation could be developed only in the *o*- or *p*-position, as is soon shown by a consideration of possible contributors to the respective hybrid intermediate structures. Since the acetamido-group alone does not produce the necessary activation and electron-attracting groups inhibit the reaction entirely, electrophilic substitution in a position *ortho* to an electron-releasing group such as methyl or alkoxyl seems the most likely mechanism. In partial confirmation, acetomesidide, with two positions *meta* to the

acetamido-group highly activated to electrophilic attack, gave a good yield of a product that gave correct analyses for the expected diacetoxy-derivative except that hydrolyses with 50% sulphuric acid gave only 2·5 equivalents of acetic acid.

The mechanism of the acetoxylation is being investigated.

Experimental

For general notes see the preceding paper.

Oxidation of Aceto-β-naphthalide.—(a) *In acetic acid.* Aceto-β-naphthalide (2 g.) in a little acetic acid was added to a solution of phenyl iodosoacetate (7·9 g.) in acetic acid (160 ml.). After 14 hr. at room temperature the mixture was evaporated as described in the preceding paper. Chromatography of a chloroform extract of the dry residue on alumina (60 g.) gave successively reddish-green (25 ml.), yellowish-green (80 ml.), and bright green (160 ml.) fractions; later fractions gave negligible residues. The material from the first two fractions crystallised from acetone as yellow plates (850 mg.), m. p. 206°, undepressed in admixture with 2-acetamido-1 : 4-naphthaquinone. The reddish-green filtrate combined with the third fraction yielded green needles (40 mg.), m. p. >300°, readily soluble in hot acetone, but not further investigated. No crystalline material was obtained from the mother-liquors.

(b) *In benzene.* After 4 days at room temperature the reaction in this solvent gave 11% of the quinone as the only crystalline product.

Unsuccessful Oxidations.—Starting material (55%) was the only crystalline fraction obtained from acetanilide after 5 days' treatment with the reagent in acetic acid at 30° or (40%) from aceto-*m*-toluidide after 21 days. Aceto-α-naphthalide yielded only a series of gums after 24 hr.

*Acetoxylation of Aceto-*p*-toluidide.*—Aceto-*p*-toluidide (1 g.) was kept with phenyl iodosoacetate (3 g.) in acetic acid (100 ml.) for 24 hr. at room temperature, then worked up as usual. Chromatography on alumina (20 g.) from chloroform gave a yellow fraction the material from which (*ca.* 1 g.) was rechromatographed on alumina (30 g.) from benzene. The first (yellow) band gave a trace (10 mg.) of *2-acetamido-5-methyl-*p*-benzoquinone*, yellow needles that sublimed readily at 130—140°/0·5 mm. and then had m. p. 175° (Found : N, 7·5. $C_9H_9O_3N$ requires N, 7·8%). The bulk of the product was in the succeeding pale yellow band which gave colourless crystals, m. p. 132° from benzene–light petroleum (b. p. 70—80°), raised by sublimation at 125°/0·5 mm. to 133·5°, undepressed on admixture with 4-acetamido-2-acetoxytoluene.

This product (120 mg.) was dissolved in methanol (5 ml.), 10% aqueous sodium hydroxide (5 ml.) added, and the methanol boiled off on the water-bath. The mixture was acidified with 10N-hydrochloric acid and chilled. The white solid (40 mg.) was collected and, sublimed at 215°/0·5 mm., had m. p. 224°, undepressed on admixture with 4-acetamido-2-hydroxytoluene.

Three treatments of the acetoxy-compound in a little methanol with methyl sulphate (0·5 ml.) and 10% sodium hydroxide, extraction with chloroform, and crystallisation of the residue from benzene–light petroleum (b. p. 70—80°) gave colourless needles, m. p. 132°, undepressed in admixture with 4-acetamido-2-methoxytoluene.

*Acetoxylation of Aceto-*p*-anisidide and Phenacetin.*—Aceto-*p*-anisidide (5 g.), treated and worked up as for aceto-*p*-toluidide, gave 4-acetamido-2-acetoxyanisole (4·95 g.), m. p. 158° from benzene–light petroleum (b. p. 60—70°) (Found : C, 59·7; H, 5·3; N, 6·4. Calc. for $C_{11}H_{13}O_4N$: C, 59·2; H, 5·8; N, 6·3%). The product was converted by methyl sulphate and alkali into 4-acetamidoveratrole, m. p. and mixed m. p. 132° from benzene–light petroleum (b. p. 70—80°). Phenacetin (2 g.) gave a trace (80 mg.) of *2-acetamido-5-ethoxy-*p*-benzoquinone*, yellow needles, m. p. 216° from benzene–light petroleum (b. p. 70—80°), and subliming readily at 217° (Found : N, 7·2; OEt, 21·4. $C_8H_6O_3N{\cdot}OC_2H_5$ requires N, 6·7; OEt, 21·5%). The main product was 4-acetamido-2-acetoxyphenetole (1·55 g.), m. p. 134° after sublimation at 160°/0·5 mm. and recrystallisation from benzene–light petroleum (b. p. 70—80°) (Found : C, 61·2; H, 6·2; N, 6·2. Calc. for $C_{12}H_{15}O_4N$: C, 60·8; H, 6·4; N, 5·9%). Hydrolysis and methylation as above gave 4-acetamido-2-methoxyphenetole, m. p. 143° from benzene–light petroleum (b. p. 70—80°). Hydrolysis and ethylation with sodium hydroxide and ethyl sulphate gave 4-acetamidocatechol diethyl ether, m. p. 126° from benzene–light petroleum (b. p. 70—80°).

*Oxidation of Aceto-*o*-toluidide.*—Aceto-*o*-toluidide (2 g.) was oxidised with phenyl iodosoacetate (8·6 g.) in acetic acid (130 ml.) for 7 days at room temperature. Evaporation at the water-pump gave a yellow distillate, and steam-distillation of the residue gave a yellow crystalline solid. The combined distillates and solid were extracted with ether which was then washed with sodium carbonate solution, dried (Na_2SO_4), and evaporated. The yellow solid residue

sublimed readily from the water-bath and then had m. p. 67—68°, undepressed in admixture with *o*-toluquinone. The residue from the steam-distillation was chromatographed on alumina (40 g.) from chloroform and yielded starting material (470 mg.), m. p. and mixed m. p. 108° from light petroleum (b. p. 60—70°).

In another experiment the quinone was steam-distilled and the total distillate saturated with sulphur dioxide. Solvents were evaporated at the water-pump and the oily residue extracted with benzene, to give 43% of toluquinol, m. p. and mixed m. p. 124—125° from benzene.

Oxidation of Aceto-o-anisidide.—Aceto-*o*-anisidide (1·6 g.) was oxidised with phenyl iodosoacetate (6·2 g.) in acetic acid (100 ml.) for 24 hr. at room temperature and worked up as above. The residue chromatographed on alumina (30 g.) from benzene yielded a purplish-red eluate, the residue from the evaporation of which (460 mg.) gave colourless crystals of which the m. p. was raised to 165—167° by several recrystallisations from benzene–light petroleum (b. p. 70—80°), and further to 169·5—170° (softening from 165°) by sublimation at 145—150°/0·5 mm. (Found: C, 59·5; H, 5·8; N, 6·6; OMe, 13·1. $C_{10}H_{10}O_3N{\cdot}OCH_3$ requires C, 59·2; H, 5·9; N, 6·3; OMe, 13·9%). Chloroform eluted only dark material from the column. Treatment with warm aqueous-methanolic sodium hydroxide and acidification converted the above product into a black powder. Treatment with sodium hydroxide and methyl sulphate, and extraction with chloroform, gave an oil that crystallised from benzene–light petroleum (b. p. 50—60°) in pearly flakes which softened at *ca.* 90° and were completely molten only at 110°. Sublimation at 80°/0·5 mm. gave an initial fraction (<1 mg.) of fine needles, m. p. 81—81·5°, which was quickly followed by a fraction softening and melting progressively above 79°. Attempted fractional sublimation at 60°/0·005 mm. was unsuccessful.

In another experiment, aceto-*o*-anisidide (5 g.) yielded a chloroform-insoluble residue of orange solid (330 mg.) which could be satisfactorily recrystallised only from a large volume of boiling alcohol and then formed orange needles of 2-*acetamido*-3-*methoxy*-p-*benzoquinone*, m. p. 253—254° (decomp.) (Found: C, 55·8; H, 4·7; N, 7·4; OMe, 15·5. $C_8H_6O_3N{\cdot}OCH_3$ requires C, 55·4; H, 4·6; N, 7·2; OMe, 15·9%). Much loss occurred on recrystallisation, as the compound was decomposed by alcohol (cf. Braude, *loc. cit.*), evaporation of a solution of the pure material yielding only a dark gum from which a few crystals slowly separated. The ultraviolet absorption spectrum was rapidly determined on a freshly prepared solution in 95% alcohol.

Acetoxylation of Acetomesidide.—Acetomesidide (1 g.) was treated with phenyl iodosoacetate (4·4 g.) in acetic acid (100 ml.). After 22 hr. at room temperature the mixture was worked up as usual. The chloroform eluate yielded colourless crystals (990 mg.), probably OO'N-*triacetyl*-2 : 4 : 6-*trimethylphloramine*, m. p. 244° from ethyl acetate–light petroleum (b. p. 70—80°) [Found: C, 61·8, 61·8; H, 6·5, 6·4; N, 4·9; Ac, 37·1, 37·8% after 3 times the normal period of hydrolysis with 50% sulphuric acid; *M* (Rast), 278, 303. $C_{15}H_{19}O_5N$ requires C, 61·4; H, 6·5; N, 4·8; 3Ac, 44·1%; *M*, 293].

No identifiable product was obtained from this material by means of 10% hydrochloric acid, sodium methoxide in chloroform–methanol, sodium hydroxide and methyl sulphate, benzoyl chloride and alkali, or potassium permanganate.

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