430. *Bromo-derivatives of Pulvinic Acid.*

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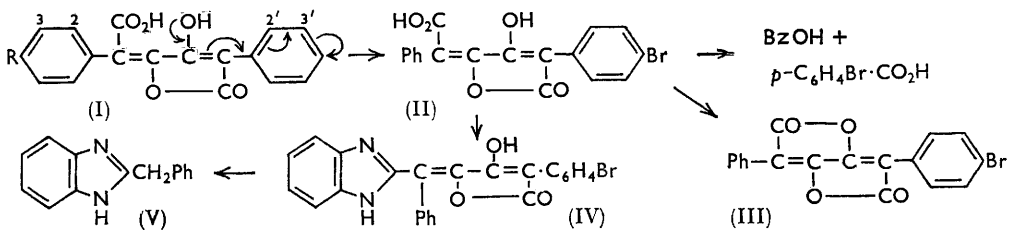
Bromination of pulvinic acid (the *trans-trans*-form) gives the 4′-bromo-derivative. The isomeric 4-bromo-compound has also been synthesised. These two derivatives give, on dehydration, the same dilactone which with methanolic potassium hydroxide affords methyl esters of *trans-trans*- and *cis-trans*-4-bromo-pulvinic acid. The constitution of the bromo-acids has been established by two methods. The stereochemistry is deduced from the relative solubilities and ultraviolet absorption spectra of the isomers.

Pinastric acid (methyl ester of I; R = OMe) has two special features: [1] (1) The position of the methoxyl group in the natural product is also that in the product formed on methanolysis of *p*-methoxypulvinic dilactone (cf. III). (2) Pinastric acid is the *cis-trans*-form,* and isopinastric acid, obtained by synthesis, is the *trans-trans*-form. We now report a study of the analogous monobromo-compounds.



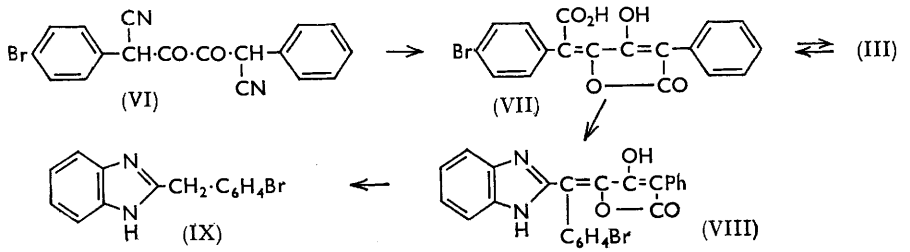
Bromination of pulvinic acid was reported by Volhard [2] though the constitution of the product was not established. Activation as indicated in formula (I) suggests that the bromine atom would enter the 4′-position and this has been proved by the following reactions of the product (II). (*a*) With neutral potassium permanganate it yielded benzoic acid and *p*-bromobenzoic acid, locating the bromine atom in a *para*-position. (*b*) Condensation with *o*-phenylenediamine and alkali-fission of the product (IV) yielded 2-benzylbenzimidazole (V).

Dehydration of 4′-bromopulvinic acid (II) by acetic anhydride yielded *p*-bromopulvinic dilactone (III). This is formed by Asano and Kameda's method [3] involving condensation

* *cis*- and *trans*- refer to the Ar·C:C·C:CAr groupings.

[1] Grover and Seshadri, *Tetrahedron*, 1938, **4**, 105, and unpublished work.
[2] Volhard, *Annalen*, 1894, **282**, 1.
[3] Asano and Kameda, *Ber.*, 1934, **67**, 1522.

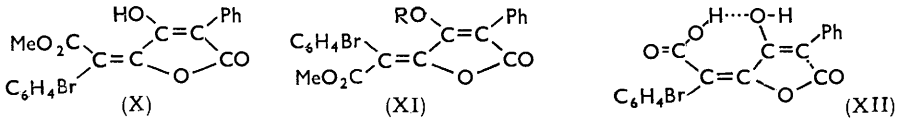
of 4-bromobenzyl cyanide successively with ethyl oxalate and benzyl cyanide, hydrolysis of the dinitrile (VI), and dehydration. The dilactone (III) with aqueous sodium hydroxide formed a single monobromopulvinic acid, obtained also by hydrolysis of the dinitrile



(VI) but different from 4′-bromopulvinic acid (II). That this is the 4-bromo-acid (VII) was confirmed as for its isomer: the *o*-phenylenediamine reaction yielded a product (VIII) which on alkali fission gave 2-4′-bromobenzylbenzimidazole (IX).

The fact that 4- and 4′-bromopulvinic acid give different benzimidazoles supports the conclusion reached for the methoxy-compounds,[1,4] that the reaction with *o*-phenylenediamine involves only the ester or carboxyl group and is free from complications.

The fission of the bromo-dilactone with aqueous sodium hydroxide, leading to 4-bromopulvinic acid (VII), seems to be controlled by electromeric effect of the bromine atom similar to that produced by the methoxy-group,[4] and the result is thus explicable. The same lactone ring opens under the action of alcoholic potassium hydroxide, and indeed of *o*-phenylenediamine as reported earlier [1] for the *p*-methoxy-compound.



The constitutions of 4- and 4′-bromopulvinic acids are supported by periodate oxidation [1] of their methyl esters. Methyl 4′-bromopulvinate (the *trans-trans*-form; see below) gave *p*-bromobenzoic acid and methyl phenylacetate; methyl 4-bromopulvinate (*trans-trans*) gave benzoic acid and methyl *p*-bromophenyl acetate.

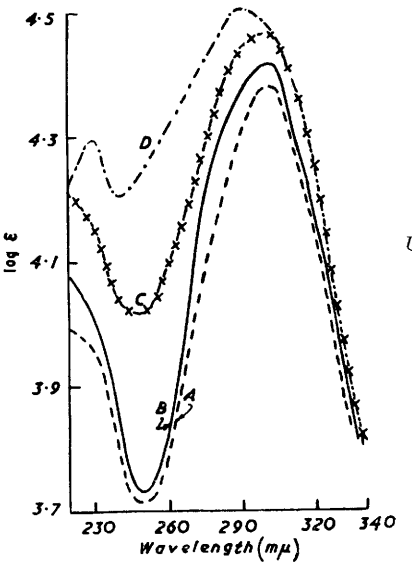
The 4-bromo-compounds showed the same type of stereoisomerism as did the *p*-methoxy-compounds (pinastric acids). The synthetic dinitrile gave on hydrolysis a *trans-trans*-acid (VII) which was obtained also as the sole product of hydrolysis of the bromo-dilactone by aqueous alkali. However, when the dilactone was treated with methanolic potassium hydroxide the product could be separated into two fractions, respectively soluble and insoluble in sodium hydrogen carbonate. The former contained esters with a free enolic hydroxyl group, whereas the latter contained the ether-esters. Each of these was separated into two fractions by crystallisation from methanol or benzene, less soluble, higher-melting *cis-trans*-fractions and more soluble, lower-melting *trans-trans*-fractions. Thus were obtained the four compounds (X; R = H or Me) and (XI; R = H or Me). The *trans-trans*-acid (VII) obtained by the hydrolysis of the dinitrile (VI) afforded the ester (X; R = H) and the ether ester (X; R = Me).

The structures thus assigned are confirmed by the ultraviolet absorption spectra. As with the pinastric acids [1] the maxima for the *trans-trans*-compounds are at longer wavelengths than for the *cis-trans*-compounds (303 mμ, compared with 290 mμ; see Figure) (in the present series also the dilactone is taken as the standard *trans-trans*-compound).

The fact that with aqueous alkali *p*-bromopulvinic dilactone gives only the *trans-trans*-acid (VII) whereas with alcoholic alkali it gives *trans-trans*- and *cis-trans*-esters and ether

[4] Mittal and Seshadri, *J.*, 1955, 3053.

esters may be of significance for the mechanism of the geometrical inversion. The acid (VII) gives a green colour with ferric chloride, indicating chelation (cf. XII) which may prevent isomeric change, whereas the ester does not give a ferric colour and so undergoes no chelation and is free for conversion into the *cis-trans*-form, in agreement with the experimental results. Further, when the *trans-trans*- and *cis-trans*-esters were hydrolysed with aqueous alkali, each gave its corresponding acid and no isomer was found.



Ultraviolet spectra (*B*) *of* p-*bromopulvinic dilactones, of methyl* 4-*bromopulvinate,* (*A*) trans-trans *and* (*D*) cis-trans, *and of* (*C*) *methyl* trans-trans-4′-*bromopulvinate, all in methanol.*

Experimental

trans-trans-4′-*Bromopulvinic Acid* (II).—Bromine (1 c.c.) was added with stirring to pulvinic acid (5 g.) in chloroform (100 c.c.). The solution was left at room temperature for 24 hr., then evaporated under reduced pressure. The *product* crystallised from acetic acid as yellow leaflets, m. p. 207—208° (3·8 g.) (Found: C, 53·1, 53·2; H, 2·8, 2·6; Br, 20·6. $C_{18}H_{11}O_5Br,H_2O$ requires C, 53·3; H, 3·2; Br, 19·8%).

Oxidation of the Acid (II).—A solution of 4′-bromopulvinic acid (0·6 g.), potassium permanganate (1·2 g.), and anhydrous sodium carbonate (0·6 g.) in water (60 c.c.) was heated under reflux for 2 hr., then cooled and acidified with dilute sulphuric acid. Sulphur dioxide was passed in until the solution was colourless. *p*-Bromobenzoic acid which separated was filtered off and, crystallised from hot water, had m. p. and mixed m. p. 250—251°. The filtrate was extracted with ether, and the extract, on concentration, yielded benzoic acid, m. p. and mixed m. p. 120—121°.

Condensation of the Acid (II) *with* o-*Phenylenediamine.*—4′-Bromopulvinic acid (1 g.), *o*-phenylenediamine (0·50 g.), and *NN*-dimethylaniline (25 c.c.) were heated at 200° for 4 hr., cooled, and poured into very dilute hydrochloric acid. The precipitate was filtered off, washed with dilute hydrochloric acid and then water. The product, 2-α-(4-p-*bromophenyl*-2,5-*dihydro*-3-*hydroxy*-5-*oxo*-2-*furylidene*)*benzylbenzimidazole*, after drying, crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as dark orange rhombohedral plates, m. p. 332—334° (decomp.) (0·39 g.) (Found: C, 61·8; H, 3·2. $C_{24}H_{15}O_3N_2Br$ requires C, 62·7; H, 3·2%).

This product (0·3 g.) was heated under reflux with 15% absolute-alcoholic potassium hydroxide (10 c.c.) for 5 hr. The insoluble potassium salts were filtered off and most of the alcohol was removed under reduced pressure. Ice-cold water (30 c.c.) was added to the residue, and the colourless solid that separated was filtered off, dried, and crystallised from ethyl acetate–light petroleum (b. p. 40—60°), giving 2-benzylbenzimidazole as plates, m. p. and mixed m. p. 185—187°.

p-*Bromopulvinic Dilactone* (III).—4′- or 4-Bromopulvinic acid (100 mg.) was heated under

reflux with acetic anhydride (5 c.c.) at 140° for ½ hr. and the clear yellow solution cooled in ice. The yellow solid that separated was filtered off, washed with a small quantity of ether, and crystallised from benzene, yielding lemon-yellow prisms of the *dilactone*, m. p. 210—212° (85 mg.) (Found: C, 59·1; H, 2·8. $C_{18}H_9O_4Br$ requires C, 58·6; H, 2·4%).

trans-trans-4-*Bromopulvinic Acid* (VII).—(i) *Ethyl* α-p-*bromophenyl*-α-*cyanopyruvate*. To a cooled solution from sodium (1·3 g.) in absolute ethyl alcohol (15 c.c.), ethyl oxalate (20 c.c.) and finely powdered 4-bromobenzyl cyanide (12 g.) were added with stirring. The mixture was heated under reflux for 1½ hr., diluted with water, and acidified with acetic acid; the colourless *ester* was precipitated. It crystallised from carbon disulphide as needles (18·0 g.), m. p. 146—147° (Found: C, 48·6; H, 3·4. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4%).

(ii) α-p-*Bromophenyl*-ββ′-*dioxo*-α′-*phenyladipodinitrile* (VI). Sodium (0·9 g.) was dissolved in absolute ethyl alcohol (15 c.c.), and the preceding ester (8 g.) was added. The stirred solution was treated with freshly distilled benzyl cyanide (4·8 c.c.) and heated under reflux for 2 hr. The red solution so formed was acidified with acetic acid and the *dinitrile* that separated was filtered off. It crystallised from acetic acid as orange leaflets (2·9 g.), m. p. 272—273° (decomp. from 257°) (Found: C, 56·2, 56·1; H, 2·7, 2·9; Br, 22·6. $C_{18}H_{11}O_2N_2Br,H_2O$ requires C, 56·1; H, 2·8; Br, 21·6%).

(iii) trans-trans-4-*Bromopulvinic acid* (VII). The dinitrile (1 g.), acetic acid (16 c.c.), concentrated sulphuric acid (8 c.c.), and water (10 c,c.) were mixed and heated under reflux for 2 hr. A yellow oil separated. The mixture was cooled, diluted with water, and stirred until the oil solidified. After filtration, the solid was treated with aqueous sodium hydrogen carbonate in which almost all of it dissolved. The mixture was filtered and the filtrate acidified with hydrochloric acid. The precipitate of 4-*bromopulvinic acid* was collected, dried, and crystallised from acetic acid, yielding light orange needles, m. p. 212—213° (0·30 g.) (Found: C, 53·2; H, 2·8. $C_{18}H_{11}O_5Br,H_2O$ requires C, 53·3; H, 3·2%). The m. p. was depressed on admixture with the 4′-bromo-isomer.

The same product was obtained when methyl 4-bromopulvinate or *p*-bromopulvinic dilactone was hydrolysed with 2% aqueous barium hydroxide or 2% aqueous sodium hydroxide respectively.

4-Bromopulvinic acid with potassium permanganate under the conditions mentioned above yielded benzoic and *p*-bromobenzoic acid.

Condensation of the Acid (VII) *with* o-*Phenylenediamine*.—4-Bromopulvinic acid (1 g.), *o*-phenylenediamine (0·5 g.), and dimethylaniline (25 c.c.) were heated at 200° for 4 hr. and worked up as given above. The product, 2-[4-*bromo*-α-(2,5-*dihydro*-3-*hydroxy*-5-*oxo*-4-*phenyl*-2-*furylidene*)*benzyl*]*benzimidazole* (VIII), crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as deep orange rhombohedral prisms, m. p. 346—348° (decomp.) (0·35 g.) (Found: C, 61·9; H, 3·1. $C_{24}H_{15}O_3N_2Br$ requires C, 62·7; H, 3·2%). The mixed m. p. with the isomer (IV) was 332°.

This product (0·3 g.) was heated under reflux with alkali as for the isomer. The product crystallised from ethyl acetate–light petroleum (b. p. 40—60°) as needles, m. p. 212—213° alone or mixed with 2-4′-bromobenzylbenzimidazole.

2-4′-*Bromobenzylbenzimidazole* (IX).—*o*-Phenylenediamine and *p*-bromophenylacetic acid (1 mol. each), heated at 180° for 2 hr., gave the *benzimidazole*, needles, m. p. 212—213° (from dilute alcohol) (Found: C, 58·1; H, 4·1. $C_{14}H_{11}N_2Br$ requires C, 58·5; H, 3·8%).

Condensation of p-*Bromopulvinic Dilactone* (III) *with* o-*Phenylenediamine*.—The dilactone (1 g.), diamine (0·48 g.), and dimethylaniline (25 c.c.) were heated under reflux for 4 hr. and worked up as above, giving the product (0·4 g.), m. p. and mixed m. p. 346—348° (decomp.), obtained similarly from 4-bromopulvinic acid, and yielding 2-4′-bromobenzylbenzimidazole with alkali.

Action of Methanolic Alkali on the Dilactone (III).—*p*-Bromopulvinic dilactone (1 g.) was dissolved in 2% absolute-methanolic potassium hydroxide (200 c.c.) and set aside for ½ hr. at room temperature, then diluted with water (200 c.c.) and acidified with hydrochloric acid. The yellow solid that separated was treated with aqueous sodium hydrogen carbonate (giving solution B) and again filtered off. The residue was fractionally crystallised from benzene. The first fraction, when recrystallised from benzene–light petroleum, separated as tiny broad prisms [*methyl* cis-trans-4-*bromopulvinate methyl ether* (XI; R = Me)], m. p. 154—156° (Found: C, 57·3; H, 3·6. $C_{20}H_{15}O_5Br$ requires C, 57·8; H, 3·6%) (the same product was obtained when methyl *cis-trans*-4-bromopulvinate was treated with an excess of methyl iodide). The second

fraction was colourless needles of *methyl* trans-trans-4-*bromopulvinate methyl ether* (X; R = Me), m. p. 110—112° (Found: C, 57·5; H, 3·5%), and was also obtained when methyl *trans-trans*-4-bromopulvinate or *trans-trans*-4-bromopulvinic acid was methylated with an excess of methyl iodide.

The solution B was acidified and the precipitate filtered off and fractionally crystallised from benzene. The first fraction crystallised as yellow rhombohedral prisms of *methyl* cis-trans-4-*bromopulvinate* (XI; R = H), m. p. 180—182° (Found: C, 56·6; H, 3·2. $C_{19}H_{13}O_5Br$ requires C, 56·8; H, 3·2%), and the second as yellow plates of trans-trans-*ester* (X; R = H), m. p. 126—128° (Found: C, 56·7; H, 3·1%).

The ester (XI; R = H) with 2% aqueous barium hydroxide yielded the *trans-cis*-acid, m. p. 226—228°. The mixed m. p. with *trans-trans*-4-bromopulvinic acid was depressed.

Each of the esters (X and XI; R = H) with *o*-phenylenediamine under the conditions mentioned above yielded the benzimidazole derivative (VIII), m. p. 346—348°, and thence 2-4′-bromobenzylbenzimidazole (IX), m. p. and mixed m. p. 213—214°.

Oxidation with Sodium Periodate.—The ester (X; R = H) (0·4 g.) in alcohol (200 c.c.) was treated with saturated aqueous sodium periodate (5 mol., 1 g.) and left at room temperature for 30 hr. Alcohol was distilled off under reduced pressure, water added to the residue, and the solution extracted with ether. This solution was extracted with aqueous sodium hydrogen carbonate (giving solution A); subsequent extraction with 1% aqueous sodium hydroxide did not remove any substance. The ether solution containing the neutral fraction was dried (Na_2SO_4) and evaporated, yielding an oil which on hydrolysis with 5% aqueous sodium hydroxide (20 c.c.), acidification, and ether-extraction gave a colourless semi-solid. This was converted into the amide, m. p. 192—194°, which agreed in properties (including mixed m. p.) with *p*-bromophenylacetamide.

Fraction A on acidification and ether-extraction gave a semi-solid. A portion of it on vacuum-sublimation gave benzoic acid, m. p. and mixed m. p. 120—121°. The crude product, on circular paper chromatography with butanol saturated with ammonia (Bromophenol Blue as indicator), showed two rings having R_F 0·59 and 0·30 at 28° identical with those of benzoic acid and oxalic acid respectively.

Methyl trans-trans-4′-*Bromopulvinate.*—This *ester* was prepared by heating 4′-bromopulvinic acid (1 g.) in acetone with dimethyl sulphate (1 mol., 0·27 c.c.) and potassium carbonate for 3 hr. and crystallised from methanol as yellow needles, m. p. 130—132° (Found: C, 56·9; H, 3·7. $C_{19}H_{13}O_5Br$ requires C, 56·8; H, 3·2%).

This ester (0·4 g.) in alcohol (200 c.c.) was treated with sodium periodate (5 mol., 1 g.) as in the previous experiment. The fraction soluble in sodium hydrogen carbonate solution *p*-bromobenzoic acid, m. p. 250—251°, and the neutral fraction with aqueous alkali yielded phenylacetic acid (*p*-toluidide, m. p. and mixed m. p. 134—136°).

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