The final product distilled at 108° at 1.4 mm. It was a yellowish oil which darkened rather rapidly.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 73.97; H, 7.84.

The melting points and the analyses of other α-acetyl-δ-keto esters, similarly prepared, are given in Table I. In each case, saponification indicated about 90% of the cyclic ester in the crude cyclized product.

Summary

The preparation of 3,4-methylenedioxyphenyl substituted α-acetyl-δ-keto esters in pure form and in good yield is outlined. A method of their cyclization which yields cyclohexenone esters of high insecticidal activity with a minimum of splitting of the ester group is described.

Furyl substituted α-acetyl-δ-keto esters were prepared and cyclized to cyclohexenone esters and were found to be of much lower insecticidal activity than the 3,4-methylenedioxyphenyl substituted products.

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Synthetic and Degradative Studies in the Isoquinoline Series. III

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In previous communications[1,2] the structure of different 1,3-dimethyl-6,7-dialkoxy- and aralkoxyisoquinolines (Ia-If), of 1-benzyl-3-methyl-6,7-methylenedioxyisoquinoline (II), synthesized by us,[3,4] was established by exhaustive methylation followed by oxidation. In all cases investigated by us, degradation gives rise either to metahemipinic acid (IIIa), or to hydrastic acid (IIIb). To complete our first paper,[1] the structure of 1,3-dimethyl-6,7-methylenedioxyisoquinoline[5] (Ig) is now ascertained, by preparing it from the 6,7-dihydroxy derivative Ia of known structure.[1] Ring closure of α-(3,4-disubstituted phenyl)-β-acylaminopropanols to the isoquinolines takes place, consequently, in all cases studied by us in *m,p*-position to the alkoxy groups, to form 6,7-disubstituted 3-methylisoquinolines, independently of the substituents.

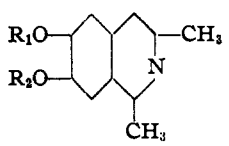
Pfeiffer, *et al.*,[6] obtained from brasiline a compound and suggested for its structure IV 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline by analogy with the structure of the compound obtained by them from hematoxyline. They attempted to confirm its constitution by synthesis from α-(3,4-dimethoxyphenyl)-β-(2′-carbethoxy-oxy-4′-methoxybenzoylamino)-propanol. Ring closure yielded only a small amount of an oily phenolic isoquinoline; its picrate was, however, not identical with that of the compound obtained from brasiline. Ring closure of the amorphous α-(3,4-dimethoxyphenyl)-β-(2′,4′-dimethoxybenzoylamino)-propanol led to a crystalline isoquinoline isomer, but which was not identical with the methyl ether of the compound from brasiline. Therefore they assign structure V, 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-7,8-dimethoxyisoquinoline, to the synthetic isoquinoline.

The present work was undertaken to synthesize through crystalline, well-defined intermediates the same phenolic isoquinoline whose picrate was described by Pfeiffer, *et al.*[6] As the structure of this synthetic compound and of its isomer have not been confirmed by degradation, it seemed desirable to carry out the oxidative degradation of the former.

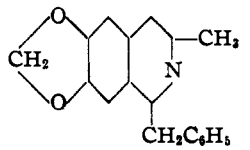
We started with the stereoisomeric α-(3,4-dimethoxyphenyl)-β-aminopropanols. One of these (m. p. 128°) was prepared according to Bruckner[5]; another (m. p. 138°) according to Iwamoto and Hartung.[7] 2-Benzyloxy-4-methoxybenzoic acid was prepared from β-resorcylic acid *via* methyl 2-hydroxy-4-methoxybenzoate and methyl 2-benzyloxy-4-methoxybenzoate. On condensation of 2-benzyloxy-4-methoxybenzoyl chloride with the aminopropanol (m. p. 138°) the amide VI is formed; on ring closure it yielded smoothly the corresponding isoquinoline derivative (benzyl ether of IV). The stereoisomeric aminopropanol gave on a similar treatment the identical isoquinoline. The benzyloxyisoquinoline derivative afforded on hydrogenolysis (Pd charcoal) the crystalline hydroxyisoquinoline IV in nearly quantitative yield. Its picrate shows m. p. 275°; its methyl ether prepared by diazomethane, m. p. 144°; its methyl ether picrate, m. p. 231–232°. The same data are recorded by Pfeiffer, *et al.*[6], for the compound formulated by them as V (*cf.* table of m. p.'s), they are consequently identical, whereas the product obtained from brasiline is different.

As a degradative approach to the structure of this phenolic isoquinoline we have chosen the oxidation with alkaline permanganate. Metahemipinic acid alone could be detected as a fragment, identified by its m. p., analysis and conversion into its ethylimide (m. p. 228°). For the synthetic hydroxyisoquinoline derivative the structure 1-

(1) Bruckner, Kovács and Kovács, *Ber.*, **77**, 610 (1944).
(2) Bruckner, Kovács and Nagy, *ibid.*, **77**, 710 (1944).
(3) Bruckner and Fodor, *Ber.*, **71**, 541 (1938).
(4) Bruckner and Krámli, *J. prakt. Chem.*, [2] **145**, 291 (1936).
(5) Bruckner, *Ann.*, **518**, 235 (1935).
(6) Pfeiffer, Breitbach and Scholl, *J. prakt. Chem.*, [2] **154**, 157 (1940).
(7) Iwamoto and Hartung, *J. Org. Chem.*, **9**, 513 (1944).

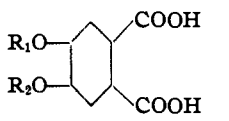


I



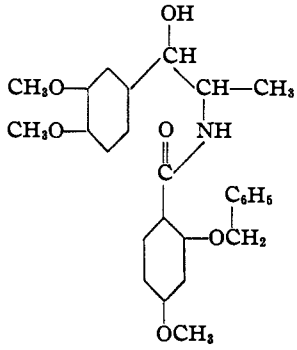
II

$R_1 = R_2 = H$/a/
$R_1 = R_2 = CH_3$/b/
$R_1 = R_2 = C_2H_5$/c/
$R_1 = R_2 = C_6H_5CH_2$/d/
$R_1 = CH_3$; $R_2 = C_2H_5$/e/
$R_1 = CH_3$; $R_2 = C_6H_5CH_2$/f/
$R_1 + R_2 = CH_2$/g/

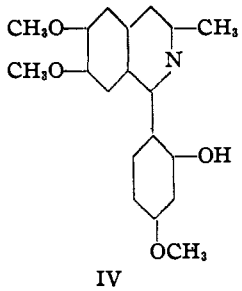


III

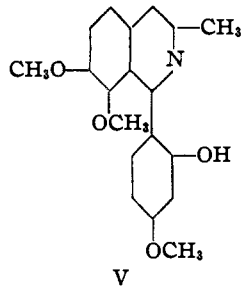
$R_1 = R_2 = CH_3$/a/
$R_1 + R_2 = CH_2$/b/



VI



IV



V

(2'-hydroxy-4'-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV is thus proved; its formulation as the 7,8-dimethoxyisoquinoline derivative V suggested by Pfeiffer, *et al.*[6], is evidently erroneous, the ring closure taking place in these cases also in *m,p*-position to the alkoxy groups.

Moreover, as the product obtained from brasiline is not identical with 1-(2'-hydroxy-4'-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV, it remains to decide whether the difference is to be found in the isoquinoline nucleus or in the radical attached at position 1.

TABLE I

MELTING POINTS OF THE ISOQUINOLINES, °C.

Compound	From brasiline, °C.	Synthesized, °C. By Pfeiffer	By us
Phenolic isoquinoline	188–189	.....	143–144
Picrate	224–225	272–275	274–276
Methyl ether	110	144–145	142–144
Methyl ether picrate	212–215	233–235	232–235

Experimental

1,3-Dimethyl-6,7-methylenedioxyisoquinoline (Ig).—A mixture of 0.6 g. (0.003 mole) of 1,3-dimethyl-6,7-dihydroxyisoquinoline (Ia) in 60 ml. of ethanol, 0.18 g. (0.0078 atom) of sodium in 5 ml. of ethanol and 1.26 g. (0.004 mole) of methylene iodide was refluxed for six hours. The non-phenolic part was isolated in the usual manner: yield, 0.28 g. of Ig, m. p. 144°, alone and mixed with an authentic specimen.[5]

α-(3,4-Dimethoxyphenyl-) β-aminopropanol. A. From O-Methylisoeugenol-ψ-nitrosite the free base was obtained (m. p. 128°). **B. From α-Isonitroso-3,4-dimethoxypropiophenone,**[8] principally by the same method as recorded by Iwamoto and Hartung[7] the base, m. p. 138°, resulted.

Methyl 2-Hydroxy-4-methoxybenzoate.—Fifteen and five tenths grams (0.1 mole) of β-resorcylic acid was dissolved in a solution of 16.8 g. (0.3 mole) of potassium hydroxide in 100 ml. of water; then 20 ml. (0.2 mole) of dimethyl sulfate added under stirring. The mixture was heated one hour on the steam-bath. The aqueous layer was decanted, the ester dissolved in 50 ml. of ether, washed with water, dried and the solvent removed. The brown oily residue was dissolved in 40 ml. of methanol, 20 ml. of concentrated sulfuric acid added and refluxed for two hours, then cooled with an ice–salt mixture, the separated crystals filtered, washed with water until neutral; yield 11 g. (59%) of colorless plates, m. p. 50–52°.[9]

2-Benzyloxy-4-methoxybenzoic Acid.—A mixture from 2.3 g. (0.1 atom) of sodium in 100 ml. of ethanol, 18 g. (0.1 mole) of the ester obtained above and 13 ml. (0.1 mole) of benzyl chloride was refluxed for twelve hours, and the resulting solution of the benzylated ester boiled with 6 g. (0.11 mole) of potassium hydroxide in 20 ml. of water for saponification. The benzylated acid was isolated by the usual manner: yield 12 g. (47%). Recrystallization from 40 ml. of ethanol yielded 9.5 g. of colorless prisms, m. p. 103°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.47. Found: C, 69.61; H, 5.51.

α-(3,4-Dimethoxyphenyl)-β-(2'-benzyloxy-4'-methoxybenzoyl-amino)-propanol (VI).—Nine and a half grams (0.037 mole) of the foregoing acid was suspended in 20 ml. of toluene, treated with 16 ml. of thionyl chloride, heated on a water-bath at 35–40°, until hydrogen chloride evolved. The thionyl chloride was removed *in vacuo*, the remainder dissolved in 50 ml. of hot absolute toluene. The crude product is satisfactorily pure for use in acylation process. Twenty-one and three-tenths grams (0.1 mole) of the aminopropanol above (m. p. 138°) was dissolved in 500 ml. of boiling anhydrous toluene, and there was added, drop by drop under vigorous stirring, the toluenic solution of 2-benzyloxy-4-methoxybenzoyl chloride prepared above. The hydrochloride of the aminopropanol separates instantaneously. The mixture was then refluxed for fifteen minutes and filtered hot: yield 13 g. (0.052 mole) of aminopropanol hydrochloride. The filtrate (washed twice with 100 ml. of 2 *N* hydrochloric acid, then with 100 ml. of 2 *N* sodium hydroxide and finally with water) was dried and concentrated to 180 ml. On cooling, the amide separated as colorless needles: yield 15.1 g. (91%), m. p. 139–140°.

Anal. Calcd. for $C_{26}H_{29}O_6N$: C, 69.16; H, 6.47. Found: C, 68.96; H, 6.26.

1-(2'-Benzyloxy-4'-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (Benzyl Ether of IV). A.—Fourteen and a half grams (0.032 mole) of the amide VI was dissolved in 300 ml. of hot toluene, then 15 ml. of phosphoryl chloride added on heating and occasional stirring. The mixture was refluxed for an hour, the isoquinoline salt formed being partly precipitated during this time. The reaction mixture was allowed to cool, then exhaustively extracted with one liter of water, cleared with charcoal, filtered and made alkaline with 5 *N* potassium hydroxide. The separating oily free base solidifies on standing in the ice-box overnight. The crude product was washed with water and dried, yield 10 g. (75%) of a yellow microcrystalline powder. On recrystallization from 180 ml. of

(8) Karg, *Arch. Pharm.*, **282**, 49 (1944).
(9) Mutschler, *Ann.*, **185**, 222 (1877).

alcohol–water (1:8), delicate needles, m. p. 83–84°, resulted. The hydrochloride prepared by the customary method forms a yellowish green crystalline powder, m. p. 221–222°.

Anal. Calcd. for $C_{26}H_{25}O_4N\cdot HCl$: C, 69.10; H, 5.79. Found: C, 69.10; H, 5.88.

B.—From 0.4 g. (0.002 mole) of the aminopropanol (m. p. 128°) in 15 ml. of toluene and 0.16 g. (0.0006 mole) of acid chloride—in the manner described above—0.3 g. of an amorphous amide was obtained which could be converted without further purification into the isoquinoline derivative. It yielded 0.2 g. of snow white clusters of crystals, m. p. 68°, which rises on recrystallization to 81°, alone and in admixture with the specimen obtained under A (its hydrochloride melted alone and mixed with that of A at 219–221°).

1-(2′-Hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline. IV.—Fifteen grams (0.033 mole) of the benzyloxyisoquinoline in 300 ml. of anhydrous ethanol absorbed 825 ml. of hydrogen (Pd charcoal) (calcd. for 1 mole H per mole, 809 ml.). The yellowish green crude product (10.75 g.) was recrystallized from aqueous ethanol to give 7.25 g. of delicate needles, m. p. 143–144°. This, together with a further crop (3.1 g.) of needles of the same m. p., yielded 10.35 g. (96%), equally soluble in cold dilute alkali and acid.

Anal. Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.88. Found: C, 69.48; H, 5.38.

The free base was converted into the **hydrochloride**, forming yellowish needles, m. p. 271°.

Anal. Calcd. for $C_{19}H_{19}O_4N\cdot HCl$: C, 62.89; H, 5.56. Found: C, 62.64; H, 5.62.

Picrate.—Yellowish microcrystals, m. p. 274–276° (dec.). Pfeiffer, *et al.*,[6] recorded 274–275° (dec.).

Anal. Calcd. for $C_{25}H_{22}O_{11}N_4$: C, 54.13; H, 4.00. Found: C, 54.25; H, 3.95.

1-(2′,4′-Dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (Methyl Ether of IV).—Twenty-six-hundredth gram (0.001 mole) of the phenolic isoquinoline IV dissolved in 10 ml. of anhydrous methanol was methylated by means of a 0.5 *N* ethereal diazomethane solution, until the yellowish color of the latter did not disappear: colorless plates, m. p. 144°. Pfeiffer[6] recorded m. p. 143–144°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24. Found: C, 70.42; H, 6.19.

Picrate.—Yellow plates, m. p. 231–232° (dec.). Pfeiffer[6] recorded m. p. 232–235°.

Anal. Calcd. for $C_{26}H_{24}O_{11}N_4$: C, 54.91; H, 4.26. Found: C, 55.01; H, 4.33.

Degradation of IV to Metahemipinic Acid.—Seven and twenty-four-hundredth grams (0.022 mole) of IV and 3 g. (0.075 mole) of sodium hydroxide were dissolved in 1.1 liter of hot water, then 50 g. of potassium permanganate in one liter of hot water was added by dropping within ten minutes under vigorous stirring and heating on the steam-bath, the solution becoming after twenty minutes nearly colorless. The hygroscopic solid residue of the solution was treated twenty-four hours continuously in a Soxhlet extractor with ethanol, the solvent removed *in vacuo* to give 1.5 g. of a yellowish crystalline mass. This was dissolved in 10 ml. of water, cleared with charcoal, filtered and then acidified (nitric acid) to congo. After the solution has been neutralized with ammonia, the lead salts were precipitated by means of lead acetate at *p*H 7–8, separated in the centrifuge, washed with a small amount of water. The acid was liberated with hydrogen sulfide, the filtrate concentrated to 3 ml. and allowed to stand overnight in an ice-box; 72 mg. of brief needles was obtained, which melted alone and in admixture with metahemipinic acid at 175–177°. For the analysis it was twice recrystallized from water.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.45. Found: C, 52.66; H, 4.34.

Further identification was made converting 26 mg. of the acid into its ethylimide on treatment with 1 ml. of 25% aqueous ethylamine. The water was then evaporated the remainder sublimed *in vacuo*, and 23 mg. of crystals obtained. Recrystallization afforded colorless long needles, m. p. 228°.[10] The ethyl imide of hemipinic acid shows m. p. 93°.[11]

Anal. Calcd. for $C_{12}H_{13}O_4N$: C, 61.25; H, 5.57. Found: C, 61.50; H, 5.59.

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Summary

The ring closure of α-(3,4-dialkoxyphenyl)-resp. (3,4-methylenedioxyphenyl)-β-acylaminopropanols takes place in all cases investigated in *m,p*-position to the alkoxy groups, to form 6,7-disubstituted 3-methylisoquinolines. This is supported by a study of the oxidative degradation even in the case of 1-(2′-hydroxy-4′-methoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline IV first obtained as picrate by Pfeiffer, *et al.*,[6] and described erroneously as a 7,8-dimethoxyisoquinoline derivative V. Consequently, the structure of the isomeric compound, obtained by Pfeiffer, *et al.*, from brasiline, and formulated as IV, becomes doubtful.

SZEGED, HUNGARY RECEIVED JANUARY 7, 1948

(10) Goldschmiedt, *Monatsh.*, **9**, 722 (1888)

(11) Freund and Helm, *Ber.*, **23**, 2906 (1890).