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A NOVEL PREPARATION OF BENZO(b)OXEPINS

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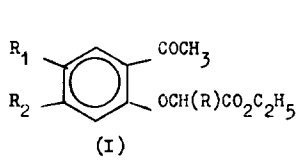
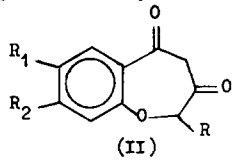
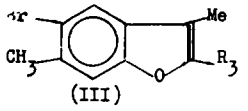
During exploratory work on the synthesis of Aplysin (1,2)ethyl α-(2-aceto-4-bromo-5-methylphenoxy) propionate (I; R = R_2 = Me ; R = Br) was found to have been partly converted by the action of



(I)



(II)



(III)

phosphorus oxychloride in benzene solution into an acidic substance, $C_{12}H_{11}O_3Br$, m.p. 111° - 112° which is formulated as 2-methyl-2,3,4,5-tetrahydro-4'-bromo-3'-methylbenzo(b)oxepin-3,5-dione (II; R = R_2 = Me ; R_1 = Br). Subsequently the same product (identical m.p. analytical and r_f data) was obtained by the action of ethanolic sodium ethoxide on I (R = R_2 = Me ; R = Br) and amongst the products of interaction of 5-bromo-2-hydroxy-4-methylacetophenone and ethyl α-bromo propionate in acetone solution containing potassium carbonate. Its production by cyclisation under acidic or basic conditions is unusual. Formulation of the new compound as a seven-membered ring substance of the oxepin series is consistent with the

following spectroscopic information: ultraviolet absorption, λ(max) (EtOH) 226 mμ (ϵ30,900), 262 mμ (11,800), 303 mμ (11,800), 328 mμ (15,800); infrared absorption (KBr) 1714 cm^{-1}(intense CO); nuclear magnetic resonance data ($CDCl_3$), 1.92 (1H), 2.92 (1H), 5.68 (1H), 5.44, 6.12 (2H), 7.56 (3H), 8.84 (3H); and mass spectral data, intense molecular ion peak, M-72 peak (due to loss of $COCH_2CO$) and other peaks in conformity with expectation The absence of the enolic form of I is in agreement with the findings of Hofmann(3) on a related compound.

Upon hydrolysis of II with ethanolic potassium hydroxide, a single acidic product was isolated namely α-(2-aceto-4-bromo-5-methylphenoxy) propionic acid m.p. 136° - 137°. Reduction of II with sodium borohydride gave an oily diol, λ(max) (EtOH) 280 mμ , ν_{OH} intense, ν_{CO} nil, similar in light absorption to the reduction product of ethyl 2-aceto-4-bromo-5-methylphenoxy propionate (I; R = H, R_1 = Br, R_2 = Me) showing interruption of the conjugation to have occurred. II gave a 2:4-dinitrophenylhydrazone m.p. 259° - 260° (decomp.) with ultraviolet absorption λ(max) ($HCONMe_2$) 390 mμ and a less well-defined semicarbazone, m.p. 184° - 186°.

2-methyl-2,3,4,5-tetrahydrobenzo(b)oxepin-3,5-dione (II; R_1 = R_2 = H ; R = Me) m.p. 33° - 34° * was obtained by cyclisation of ethyl α-(2-acetophenoxy) propionate and possessed properties consistent with this formulation.

In view of the preceeding results it was of interest to examine in greater detail the cyclisation of o-acetophenoxyacetates,

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* Correct analyses were obtained for compounds described all of which are new substances.

one of the classical routes to the benzofurano system. Cyclisation of ethyl 2-aceto-4-bromo-5-methylphenoxyacetate (I; R_1 = Br, R_2 = CH_3, R = H) with ethanolic sodium ethoxide and an extraction procedure similar to that used for the C - CH_3 compound led to the formation of ethyl 5-bromo-3,6-dimethyl-coumarilate (III; R_3 = CO_2Et), the corresponding coumarilic acid (III; R_3 = CO_2H), 5-bromo-3,6-dimethylcoumarone (III; R = H) together with a small proportion of a product m.p. 162° - 164° purified by preparative TLC, and formulated as 2,3,4,5-tetrahydro-4'-bromo-3'-methylbenzo(b)oxepin-3,5-dion (II; R_1 = Br, R_2 = CH_3, R = H) in view of its UV, IR absorption, r_f value and mass spectral data (parent molecular ion 268). It would appear that the occurrence of compounds of this type in the internal Claisen condensation procedure has been overlooked formerly due to the small proportion present or to hydrolysis during processing or both. By the interaction of ethylbromomalonate with o-hydroxyacetophenone followed by cyclisation the 2-carboethoxyl derivation of the parent compound (II; R = R_1 = R_2 = H) was obtained. Ketonic hydrolysis caused some ring scission, although the formation of 3-methylcoumarilic acid was reduced.

No previous cyclisations of this type have been described. The route is essentially simpler than the existing procedures (3,4,5,6,7) for the derivation of tetrahydro compounds in the series and experiments on the conversion of the previous compounds to their aromatic analogues are in progress. Indications have been obtained that the same type of procedure is applicable to the preparation of azepins, thiepins and the methylenic analogue of II.

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