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THE SYNTHESIS OF 3-SUBSTITUTED FLAVONES FROM FLAVONOLS

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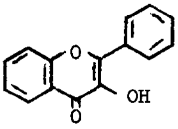
We wish to report a synthetic procedure in which the 3-hydroxyl group of flavonol 1 is replaced by a carbon atom. Compounds 6, 10A, 10B, and 12 have been prepared in this sequence. The key intermediate between 1 and these products is the flavandione 2. Flavonols occur widely in nature and are readily synthesized. The development of these and related sequences should provide new synthetic opportunities for flavonols.

The flavandione 2 is readily prepared from 1 by periodic acid in methanol.[2] The product isolated from the reaction mixture is the 3-hemiketal of 2, namely compound 3, a colorless solid. However, solutions of 3 are always yellow indicating the presence of the free dione 2.



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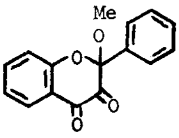

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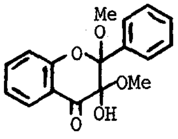

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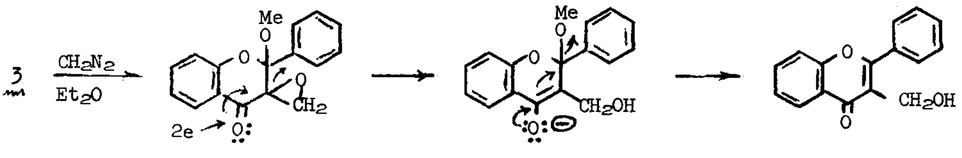
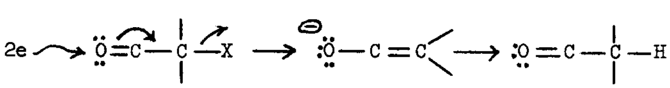
The diketone derivative 3 reacts with diazomethane in ether to form the epoxide 4.[3] We attempted to deoxygenate the epoxide 4, to the methylene compound 8 (Z=H) using a mixture of

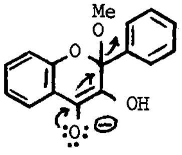


4 5 6

zinc, sodium iodide, sodium acetate and acetic acid. Cornforth[4] had used this reagent to deoxygenate epoxides in his synthesis of squalene. However, our product was 3-hydroxymethylflavone 6, recently prepared by Hofmann[5] from 3-bromoflavanone, formaldehyde and base in methanol. In our reactions, we found the presence of the iodide superfluous, zinc and acetic acid alone effecting the conversion.

There are several ways to account for this result. The one we present rationalizes this reaction and subsequent ones and finds analogy in mechanisms proposed for α-substituted ketones. In general, ketones are not readily reduced by zinc and acetic acid. Notable exceptions are ketones with alpha substituents. The mechanism below has been suggested where X may be halogen, amino, hydroxy or acyloxy.[6] In our case the reaction can be visualized as proceeding through the intermediate 5 as depicted above, the α-substituent being the epoxy oxygen at C-3.





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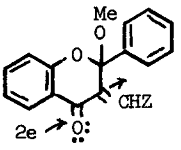
Several years ago, we had observed that the dione derivative was readily reduced to 1 by hydrogen iodide. This trivial result is now recognized as a manifestation of the same kind of reaction. Zinc and acetic acid effects the reaction and we postulate the intermediate corresponding to 5 as 7.

The formation of the flavone ring system in 1 and 6 depends upon three factors. First there must be a tender bond exo to the heterocyclic ring at C-3. In the case of 4 it is the carbon oxygen bond of the epoxide. In the case of 2, present in solutions of 3, it is the carbonyl at C-3. Secondly, the methoxyl group of C-2 becomes very labile as a result of its increased allylic character in the intermediates 5 and 7. Finally, the end product, a flavone, is a very stable heterocyclic system. Thus, its carbonyl absorbs above 6μ in the ir and is inert toward most of the normal ketone reagents.[7]

The carbonyl at C-3 of the dione 2 is sufficiently reactive to form normal Wittig products with carbonyl stabilized phosphoranes and these products should lend themselves to the synthesis. The carbethoxy- and benzoyl- derivatives 8A and 8B have been prepared by refluxing 3 with the appropriate phosphoranes in ethanol.[8] These substrates contain a reactive exo carbon-carbon double bond at C-3. Accordingly, we were not surprised when zinc and acetic acid reduced these



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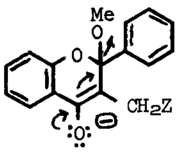

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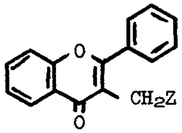

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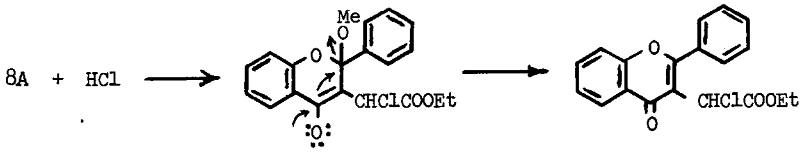
A
Z = COOEt

B
Z = COPh

to the 3-substituted flavones 10A and 10B. Presumably, the intermediates were 9A and 9B.

Finally, it occurred to us that 8A might undergo a Michael addition with HCl to form the adduct 11 which would then collapse to the flavone 12. Our expectations were realized.



11

12

Compounds 8A, 8B, 10A, 10B and 12 are new compounds. The assigned structures are supported by ir and nmr spectra and elemental analyses. In the reductive steps, 500 mgms each of reactant and zinc were heated on a steam bath with 10 ml of AcOH for 1 hr. Workup involved filtration of the zinc, evaporation of the solvent and recrystallization. The yields (isolated crude product) and melting points are reported in Table I.

TABLE I

Yields and Properties of 3-Substituted Flavones

Reaction	% Yields	m.p. Products
3 → 1	84%[a]	166-7° (lit. 169°)
4 → 6	54%	161-2° (lit.[5] 160-3°)
8A → 10A	46%	102-2.5° (CCl_4)[b]
8B → 10B	42%	124° ($EtOH/H_2O$)[b]
8A → 12	60%[c]	122-3° (EtOH)[b]

a). Pour filtered AcOH solution into H_2O and collect precipitated flavonol.

b). m.p. is for the analytical sample (solvent for recrystallization).

c). 500 mg 8A, 5 ml EtOH, 15 drops conc HCl, reflux 1 hr., cool, filter.

References

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