REGULARITIES IN BIOLOGICAL ACTIVITY AMONG DERIVATIVES OF CHROMONE AND 4-OXOPYRIMIDINE

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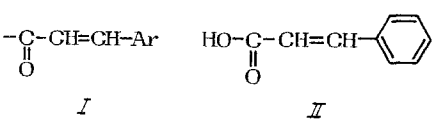
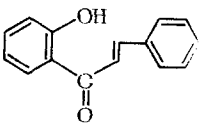
An extensive body of information now exists on the biological activity of naturally occurring cinnamic acid and chromone derivatives and their synthetic analogs. In comparing the various kinds of activity of these groups of compounds the important fact that derivatives of cinnamic acid and chromone (flavonoids) display pronounced antioxidant activity [1, 5, 6] merits particular attention. It is thought that the antioxidant activity of these compounds stems from their ability to neutralize active forms of oxygen and to cut off free radical processes in the chain [9-11], i.e., they act as free radical absorbers. Although from the chemical classification standpoint cinnamic acid derivatives and flavonoids constitute different types of compounds, they should still be grouped together in terms of their pharmacological characteristics.

In comparing and analyzing the biological properties of these groups of compounds, it can thus be seen that the common structural characteristic is the cinnamoyl moiety (I), which determines the configurational and conformational features of cinnamic acid (II) and the 2-hydroxychalcones (III), the biogenetic precursors of the flavones (IV) and flavonones (V).



I

II



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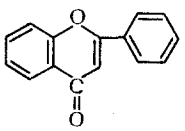

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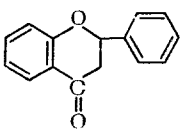

V

In our previous research [4] we have shown that these classes of compound exhibit marked antiallergic activity, the chalcones being considerably superior to the corresponding flavones in this respect. The chalcones and cinnamic acid derivatives inhibit the slow-type hypersensitivity reaction (PCAR) to an equal extent. This probably arises from the fact that the chalcones constitute a system with an open conjugated chain and are therefore structurally closer to cinnamic acid. It should also be remembered that in both groups the vinylene fragment has a trans-configuration. The heterocyclization of the chalcones to the corresponding flavones produces a rigid, closed conjugated system, in which the possibility of configurational and conformational transitions is excluded. Our earlier experimental studies [2, 4] revealed that when the cinnamoyl moiety vinylene group was hydrogenated to yield hydrocinnamic acids and dihydrochalcones, antioxidant, hepatoprotective, and antiallergic properties were either reduced or disappeared altogether. A distinct dependence was observed between antioxidant, hepatoprotective, and antiallergic activity and conjugation involving the vinylene group. It is precisely the presence of the latter group in the conjugated chain that provides the transfer of electronic effects and ensures the configurational characteristics which in their turn guarantee complementarity with receptors [4].

The conclusion may be drawn from the above that the cinnamoyl moiety becomes the decisive structural characteristic and makes the greatest contribution to the kinds of activity mentioned.

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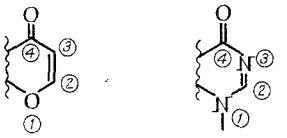
It is worthwhile investigating the regularities underlying the effect that conjugation has on the biological activity of the structurally remote derivatives of chromone VI and 4-oxopyrimidine VII. Interest in pyrimidine derivatives stems from their relationship with endogenic substances, whose number include the oxopyrimidine bases. They are responsible for the molecular mechanisms governing the storage and transfer of genetic information, and also participate in matter exchange processes, where they fulfill the role of coenzymes.

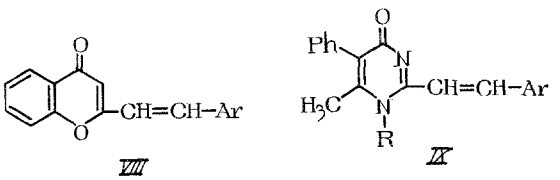
In comparing the structures of VI and VII fragments can be distinguished in which conjugation involves either carbon atoms alone (VI), or carbon and nitrogen atoms (VII).



VI VII

In the conjugated chain there is significant electron charge deficiency at position 2 in both structures due to the influence of the heteroatoms of oxygen and nitrogen having sp^2 configuration, and the carbonyl group. If a substituent were to be introduced into position 2 with the aim of lengthening the conjugated chain, the transfer of electron effects involving the C(2) and C(3) carbon atoms would be preferable for the chromones. This is explained by the greater electronegativity of the N atom with sp^2 configuration at position 3.

Previous reports [2, 4] used vinyl analogs of chalcone and chalconeacrylic acids as examples to discuss in length the dependency of biological activity on the length of the of the conjugated chain. It was shown that antiallergic activity was intensified by introducing into the conjugated chain a styryl fragment containing electron donor substituents in the aromatic ring. This served as a basis for synthesizing new vinylaryl derivatives of chromone VIII and 4-oxopyrimidine IX.

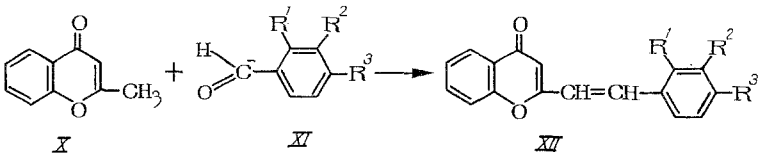


VIII IX

(R—Ar middle left)

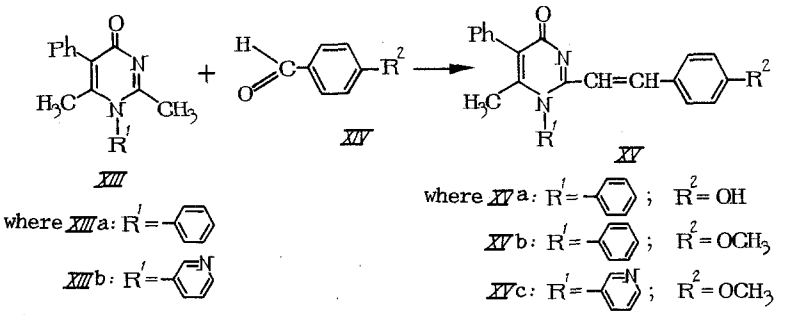
The advisability of using a styryl fragment to form a conjugated chain is evident for the following reasons: by analogy with the leukotrienes structures VIII and IX contain a conjugated chain, but one that has significant polarity due to the presence of a carbonyl group; the chromone ring, which is typical of those substances that inhibit leukotriene synthesis [7, 8], governs the high antiallergic activity of many natural and synthetic compounds [3, 4]; by and large replacement of the sp^2 C by an N atom having a similar configuration in the conjugated chain will not disturb the transfer of electronic effects, and so it may be presumed that structure IX will have antiallergic activity; from a comparison between the predicted structures of VIII and IX and those of leukotriene synthesis inhibitors it can be stated that the conjugated systems $-C(=O)-CH=CH-CH=CH-$ or $-C(=O)-N=CH-CH=CH-$ may be the deciding factors in whether compounds display antiallergic activity.

Derivatives of compounds XII (a-d) and XV (a-c), which were obtained, in line with predictions, from 2-methylchromone (X) and 2-methyl-4-oxopyrimidines XIII, are shown below.



X XV XII

where XIIa: $R^1=H$; $R^2=H$; $R^3=OH$; XIIb: $R^1=OH$; $R^2=H$; $R^3=OH$; XIIв: $R^1=H$; $R^2=OCH_3$; $R^3=OH$; XIIг: $R^1=H$; $R^2=OCH_3$; $R^3=OCH_3$;



The starting reagents 2-methylchromone (X) and 2-methyl-4-oxopyrimidine (XIII) with a phenyl radical at position 1 displayed a low PCAR* inhibition level of about 40%.

In the case of 2-styrylchromone derivatives substituents that intensify polar conjugation play an important part in raising biological activity. For compound XIIa, which has a 4'-hydroxyl group, PCAR inhibition was 74.3%. When a second hydroxy group was introduced at position 2' in compound XIIb, PCAR inhibition increased to 81.6%. With compound XIIc this figure reached 84.8%, the highest PCAR inhibition being observed for compound XIId (100%), which has two methoxyl groups at positions 3' and 4' of the styryl fragment.

Compounds XIIIa and XIIIb were used to form the conjugated chain, in accordance with predictions, for 4-oxopyrimidine derivatives. Differences in the nature of the substituents at the nitrogen atom in position 3 had a significant effect on biological activity; specifically, when the phenyl radical was replaced by a π-deficient 3-pyridyl group, PCAR inhibition rose from 38.8% (for XIIIa) to 61.5% (XIIIb). In moving from compounds XIIIa and XIIIb to derivatives XVa, XVb, and XVc further increases in PCAR inhibition were observed of 77.1, 82.8, and 85.3% respectively.

The slightly higher antiallergic activity of the 2-styrylchromones can probably be interpreted as follows: as in the case of the flavones there would appear to be decyclization of the chromone heterocyclic ring [4], as a consequence of which the resulting structure experiences an increase in the number of receptor complimentarity centers, thus intensifying biological activity. A similar process cannot be suggested for 4-oxopyrimidine derivatives.

From the findings it was concluded that the use of a styryl fragment to form a polar conjugated system similar to that of the leukotrienes plays a major part in the manifestation of antiallergic activity. This opens the way to investigating biological activity correlations between groups for the new compounds.

EXPERIMENTAL

2-Styrylchromones. A mixture of 0.03 moles of 2-methylchromone and 0.04 moles of the corresponding aldehyde was dissolved in 100 ml of dry acetic acid and heated at 130-140°C for 30 min. After the resultant precipitate had been separated, it was washed with 200 ml of diethyl ether and dissolved in ethanol. This solution was brought to boiling point, then cooled. After diluting with cold water, the resultant precipitate was filtered off, washed with water, and recrystallized from ethanol to give crystalline substances of various colors.

2-Styryl-4-oxopyrimidines. A sample of 0.01 mole of the appropriate 2-methyl-4-oxopyrimidine was dissolved in a mixture of 2 ml of dimethylsulfoxide and 3.5 ml of ethanol, then 0.01 mole of aromatic aldehyde was added. After the reaction mixture had been boiled for 1.5 h at 120°C, it was cooled and then poured into 90 ml of diethyl ether. White crystalline precipitates resulted.

The synthesized compounds were identified from elemental analysis data and from a comparison between our findings and melting points and UV and IR spectroscopy data published in the literature.

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