2-ACYLCYCLOALKANE-1,3-DIONES.

OCURRENCE IN NATURE, BIOLOGICAL ACTIVITY,
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This review systematizes information on 2-acylcyclohexane-1,3-diones and 2-acylcyclopentane-1,3-diones isolated from natural sources. Questions of their biological and chemical synthesis, their natural functions, and the biological activity that they exhibit are discussed.

In one form or another,* the 2-acylcycloalkane-1,3-dione (β-triketone) fragment (1a-c) is present in many biologically active components of medicinal plants used in the folk medicines of various countries since the most ancient times. The history of the chemical study of natural cyclic β-triketones is therefore very closely linked with the general course of the development of organic chemistry itself. The biologically active components of the resins of the fern Aspidium felix, for example, were first investigated in 1826, and usnic acid was isolated from the lichens Usnea barbata and Ramalina fraxinea in 1843. An antihelminthic extract from the African plant Hagenia abyssinica (koso), known and used since antiquity, was subjected to its first chemical study in 1839. Investigations of the biologically active components of hops, used in brewing, were begun in 1885 [1].

Early investigations led to the isolation of various 2-acylcycloalkane-1,3-diones the structures of which were unambiguously confirmed or refined, thanks to the development of spectral methods of analysis, almost a century later — in the 1950s and 1960s of the 20th century. The chemical structures of the β-triketones proved to be extremely diverse. Widely distributed among them are 2-acylcyclopentane-1,3-diones and, in particular, 2-acylcyclohexane-1,3-diones with various alkyl, aryalkyl, and alkenyl side-chains. At the same time, the cyclic part of the molecule is frequently alkyated with one or more (up to four) methyl groups (for the cyclohexane derivatives, usually at the C₄ and C₆ atoms) and/or lower alkyls (up to C₄) with both normal and branched structures. The cycloalkane ring may bear from one to three prenyl, geranyl, or farnesyl residues. In the cyclohexane β-triketones there is very frequently an additional C₅ ketone function, which may also be present in the form of an enolic methyl ether. In many cases, the 2-acylcyclohexane-1,3-diones are constituent parts of polycyclic (polynuclear) molecules.

At the present time it has been established that cyclic β-triketones are present in various natural materials, including not only plant sources but also marine invertebrates and secretions of insect glands. In spite of the multiplicity of types of biological activity characteristic of cyclic β-triketones, and the clear inadequacy of information on their biogenesis and biotransformations in vivo, the protective role that these substances play in Nature may be regarded as obvious.

*All structures are shown in the form in which they are given in the original.
The compounds of the heading are found in Nature in the form of 2-acylcyclohexane-1,3-dione and 2-acylcyclopentane-1,3-dione derivatives, the latter being relatively rare. A large number of 2-acylcyclohexane-1,3-diones with simple structures have been found in the essential oils of plants of the genera Eucalyptus, Leptospermum, Xanthostemon, Darwinia and others from the Myrtaceae family growing in Australia and New Zealand and used in folk medicine [2]. The first of this group to be discovered were angustione (2) and dehydroangustione (3a) [3, 4], isolated from Backhousia angustifolia. Leptospermone (4a) [5-7] and its minor homolog flavesone (4b) [8] and also the dihydrocinnamoyl homolog grandiflorone (4c) [9] have been isolated from various species of the Australian tea tree, Leptospermum.

Tasmanone (3b) has been identified in fresh leaves of the eucalyptuses Eucalyptus risdoni, E. linearis, E. tasmanica, and E. camfeldii [10], agglomerone (3c) in E. agglomerata and E. meckieanna [11], and xanthostemone (3d) in Xanthostemon chrysanthus [12]. The β-hydroxychalcone (5) has been isolated from Leptospermum scoparium, which is used in the treatment of dysentery, diarrhea, and skin diseases, and, recently, in some forms of cancer; according to NMR spectroscopy, (5) exists in equilibrium with the tautomer (6), which is the methyl ether of a dienolic form of a cyclohexane β-triketone [13].

A triketone of similar structure, syzygiol (7a), in which the nonaromatic nature of the ring is fixed by its gem-dimethylation, has recently been isolated from the Indonesian plant Syzygium polycephaloides (also of the Myrtaceae family) [14]. Syzygiol (7a) possesses the property of inhibiting the development of skin cancer [15].

The triketone (8), having an extremely simple structure but bearing an unusually long arylalkyl side-chain, has been isolated from some Brazilian plant species Virola ssp. [16, 17]. This compound has also been isolated from Horsfeldia glabra [18].

Syntheses of some of these natural compounds have been described in the literature. The synthesis of leptospermone (4a) by the methylation of phloroisovalerophenone (9) with methyl iodide in an alkaline medium has served to confirm its structure [7]. A scheme including the methylation of a 2-acylbenzene-1,3,5-triol (11) has likewise been used in a seven-stage synthesis of syzygiol (7a) [15]: