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GENERAL INTRODUCTION

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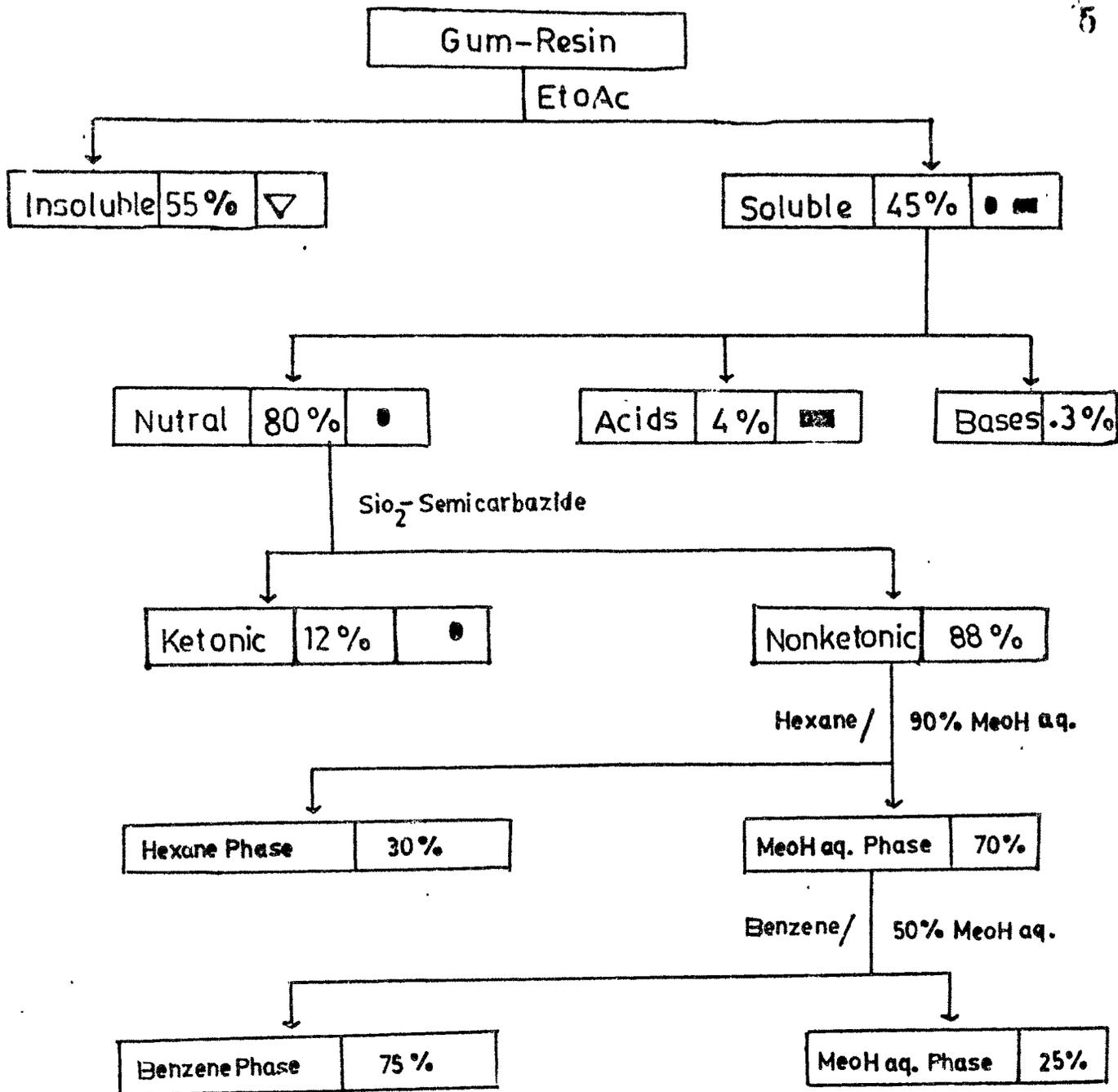
Guggulu (Sanskrit) is the gum-resin exudate from the tree Commiphora mukul, (Hook, ex stocks) Engl. (Syn Balsamodendron mukul. Hook. ex. stock), and is an article of commerce in India.¹ The classical Ayurvedic literature claims guggulu to be efficacious in the treatment of rheumatoids arthrities, obesity and allied disorders, besides indicating for it, several other therapeutic uses.² Pharmacological studies on the crude drug as well as (in some cases) on some of its fractions and pure constituents, have revealed significant anti-inflammatory, anti-rheumatic^{3,4} and hypocholesterolemic/hypolipaeamic⁵⁻⁸ activity, thus providing at least some support to the ancient claims.

Bhati⁹ was the first to examine the gum-resin from C. mukul and found that it gives some 0.4% of an essential oil, consisting chiefly of myrcene (1) and camphorene (2). Bose and Gupta¹⁰ separated the gum resin into an alcohol soluble resin (50%) and an insoluble carbohydrate gum. These workers have investigated the insoluble gum in some detail^{10,11} and have suggested a provisional structure for the purified gum. A Pakistani group²³ investigated the alcohol-soluble part by partitioning between water and ethyl ether; the non-saponifiable portion of the ether-soluble part

was shown to contain mericyl alcohol (3) and β -sistosterol (4), while the aqueous phase was demonstrated (paper chromatography) to contain the following amino acids: cystine, histidine, lysine, arginine, aspartic acid, serine, proline, tyrosine, tryptophane, valine, leucine and isoleucine.

Sukh Dev and co-workers in collaboration with the pharmacological group of Swarn Nityanand, CDRI, Lucknow, undertook a detailed investigation of the resin part of the gum-resin in an effort to track the claimed biological activity, to isolate and characterize the pharmacologically active compounds. These investigations¹²⁻¹⁸, which were complete in part only, will be summarised here.

Fig. 1 depicts the separation scheme, finally evolved for the isolation of constituents. The ethyl acetate soluble portion ("Suggulipid") carries both the hypocholesterolemic and antiinflammatory activity, while the insoluble part which represents the carbohydrate gum studied earlier by Bose and Gupta, was found to be toxic and hence, was not investigated further. The ethyl acetate fractions were further separated into bases, acids and the neutral cut. The neutral portion carries practically all the hypocholesterolemic activity, while the acids display significant antiinflammatory activity. The basic fraction shows none of these two activities. The neutral cut was further segregated into ketonic and nonketonic



Segregation Of Guggulu Gum-Resin

- : Anti-inflammatory activity
- : Hypo-cholesterolemic activity
- ▽ : Toxic

Fig. I

Fractions with the aid of semicarbazide-on-silica gel¹⁹.

Ketonic fraction

Ketonic fraction was a highly complex mixture, consisting of over two dozen (TLC, HPLC) compounds encompassing a wide range of polarity. Except for a minor constituent, tentatively identified,¹⁵ as hopenone-1 (6), all other ketones so far characterized are C₂₇ and C₂₁ steroids. The compounds identified are; Z-guggulsterol (7), (20S)-20-hydroxy-4-pregnene-3-one (8), (20R)-20-hydroxy-4-pregnene-3-one (9), guggulsterol-VI (10); Z-guggulsterone (11), E-guggulsterone (12), guggulsterol-III (13) and guggulsterol-1 (14). Z- and E-guggulsterones are the major steroids of the gum-resin constituting some 50% of the ketone fraction. These two compounds are responsible for hypolipaeamic and hypocholesteremic activities. Another group of workers have reported²⁰ the presence of ketone (15) in guggulu as well as that of the closely related triol mono-acetate (16).

Hexane phase: Hexane phase contains especially diterpenoids, besides small quantity of cholesterol (17). The compounds isolated from this phase are, cembrene-A (18) and mukulol (19).

Benzene phase: The compounds present in this phase amounts for as much as 14% of the guggulu. This material was again very complex, but it has been possible to isolate four crystalline substances, all lignans, and a waxy solid shown to be a mixture of esters derived from long chain tetrols. Of the lignans isolated, two were identified as known compounds, sesamin (20)²¹ and pluviatilol (21)²¹. The remaining two, which have been named guggulignan-I and guggulignan-II, have been tentatively assigned the structures (22) and (23) respectively.

Structure revision of the guggulignan-I forms a part of the present investigation.

The waxy solid was a mixture of esters, based on a homologous mixture of long chain tetrols (24) and ferulic acid (5). These long chain tetrols, in which C₂₀ and C₁₈ compounds were found to be by far the major ones,¹⁴ were the first reported compounds of this type in nature, though closely related biologically important phytosphingosines (25) are well-known²². Structure of the two major esters based on (24) have been established¹⁸ as (26).

Clarification of the configuration of three chiral centres of these tetrols forms a part of the present investigation.

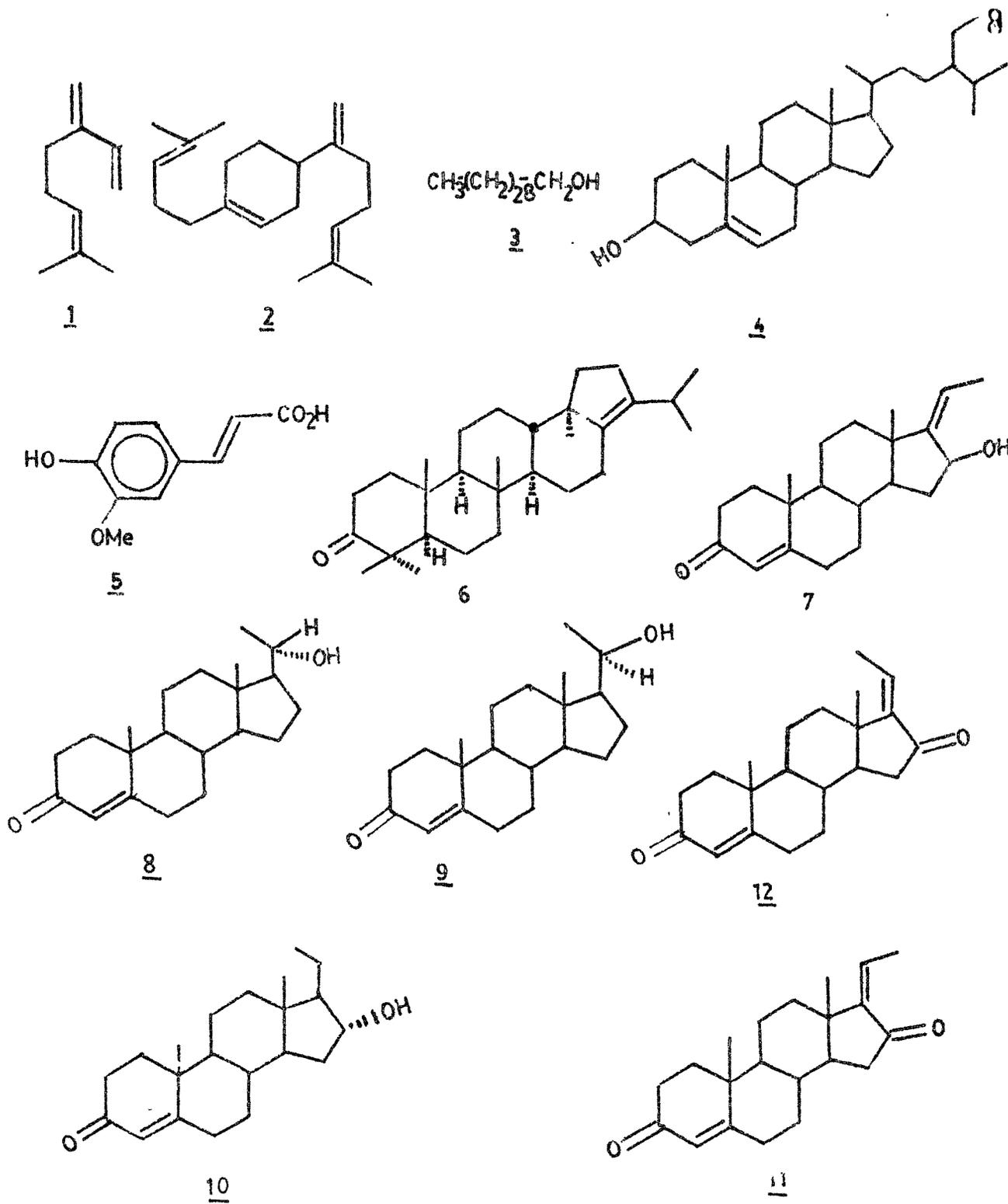


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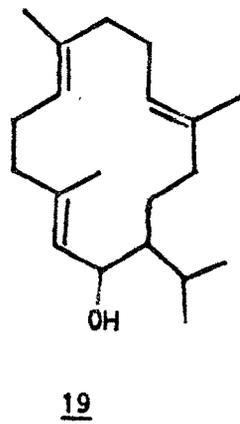
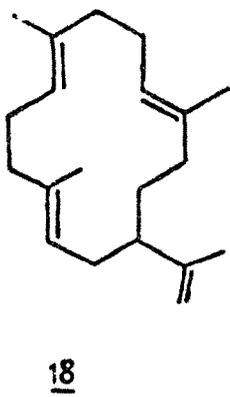
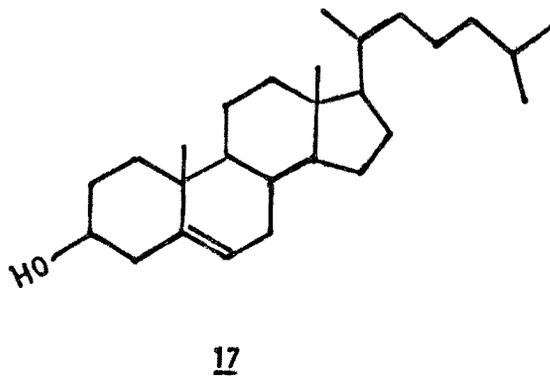
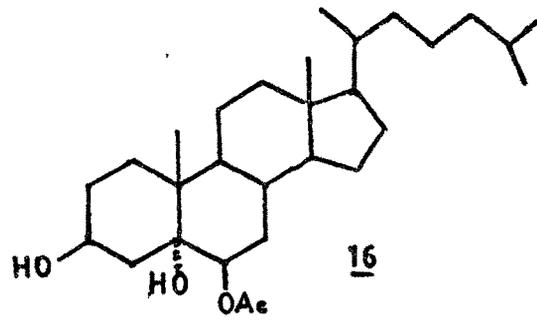
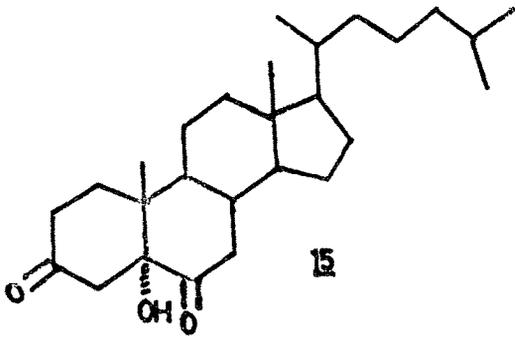
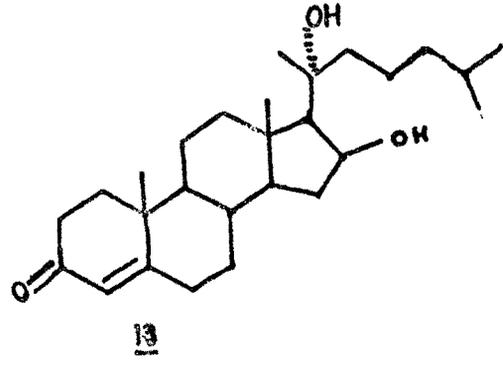
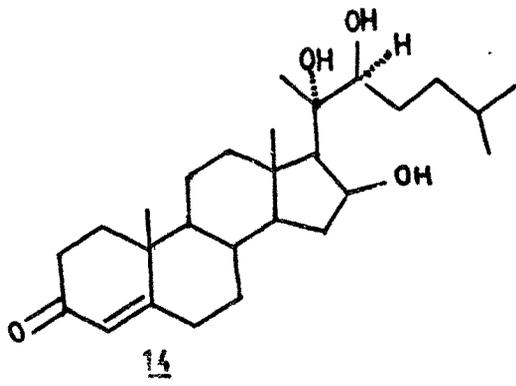
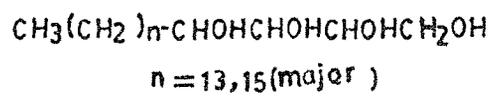
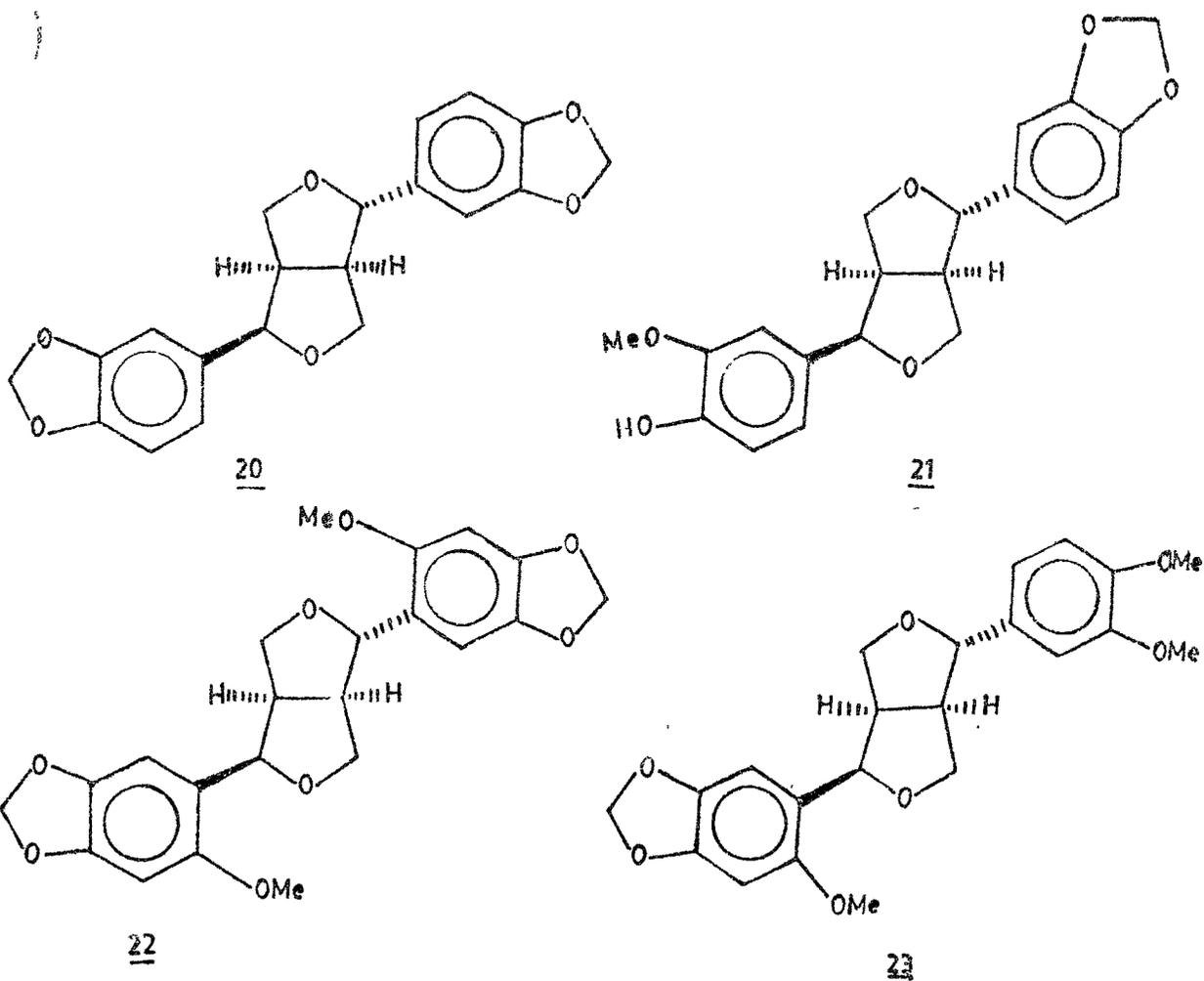
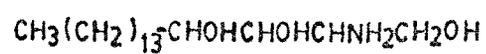


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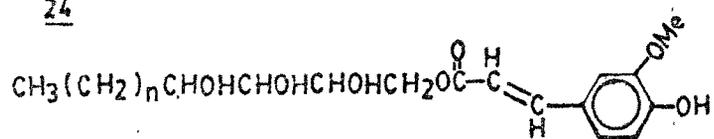


11, 12, 14, 16, 17 (minor)

24



25



$n = 13, 15$

26

The basic fraction has not been investigated chemically so far, while the acid part has been examined in only a preliminary way. The acid fraction is a complex blend of aromatic and non-aromatic acids, of which only ferulic acid (5) could be identified.¹⁸

The significant antiinflammatory activity exhibited by the acid fraction tempted us to undertake a thorough investigation of these fractions. In the present investigation many un-successful attempts were made to isolate pure constituents. Methyl esters of these acids were separated into phenolic and non-phenolic esters, each of these cuts were separated into ketonic and nonketonic by the aid of semi-carbazide-on-silica gel.¹⁹ These fractions were subjected to counter-current separation between 10% aq. methanol and pet ether. None of these fractions had tendency for separation on silica gel column. The highly complex nature of these acid fractions were demonstrated by High Pressure Liquid Chromatographic experiments. On an analytical column "Zorbax-sil", the phenacyl esters of the acids resolved into as many as 25-30 compounds. But on a preparative column "Spherosil" the separation was very poor. Because of the high complex nature and their reluctance to resolve on column, the investigation of these acid fractions was not pursued further.

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