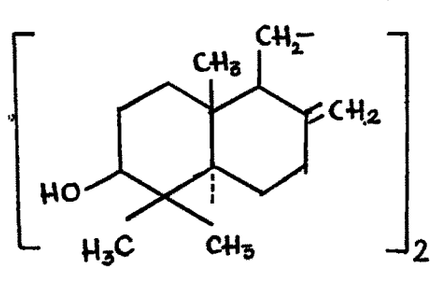
Section B — Page

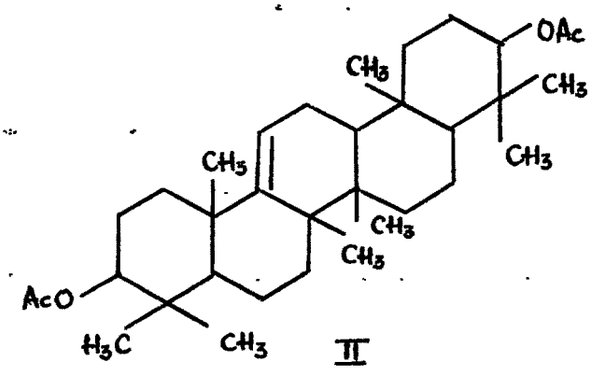
Synthesis of a tricyclic intermediate for the synthesis of triterpenoids

T H E O R E T I C A L

The chemistry of triterpenoids has recently been elucidated in most of its structural and stereochemical complexities as a result of a series of brilliant researches during the last two decades. As a result, the mechanism of the formation of these bodies, through biogenetic pathways, is now-a-days better understood. Synthetic experiments have also been quite successful leading to the synthesis of α-onocerin (I) (Stork et al, J. Amer. Chem. Soc., 1959, 81, 5516). The salient features of these synthetic studies carried out in different laboratories have been the coupling of two identical units leading to the formation of C_{30}-carbon skeleton and subsequent cyclisation to the pentacyclic system (II). (Corey et al, ibid, 1959, 81, 5259; Eschenmoser et al, Helv. Chim. Acta, 1957, 40, 1900; Barton et al, J. Chem.Soc.,



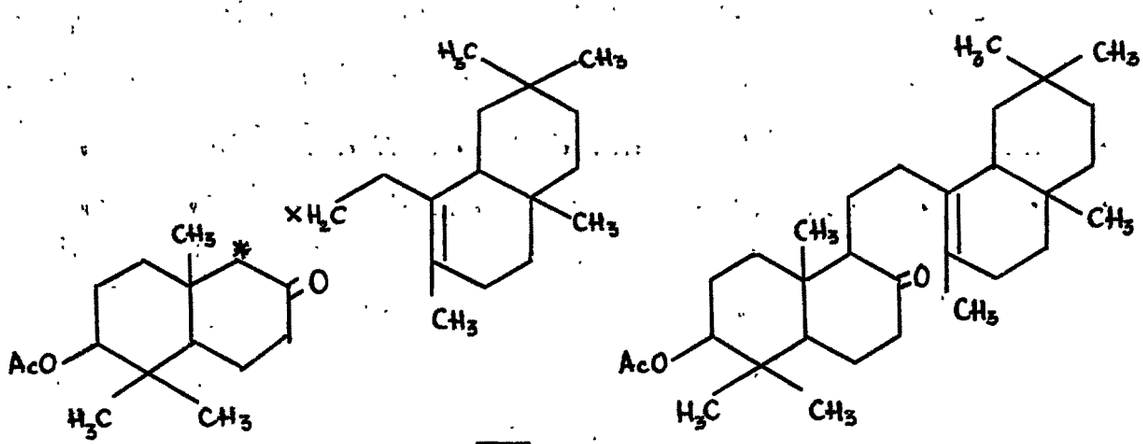
I



II

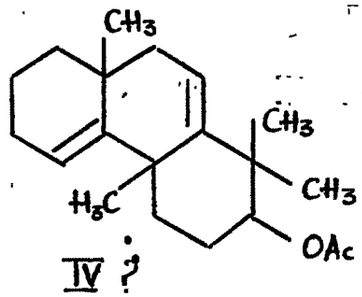
1955, 2639). Another method (Sondheimer et al, J. Amer. Chem. Soc., 1959, 81, 4429), closely related to this approach, is according to the building principle, $C_{14} + C_2 + C_{14}$, the

C_2-unit being supplied by an acetylenic moiety and C_{14}-unit represents suitably substituted α-decalones. Although these methods adumbrated above, have been highly successful for the building-up of the carbocyclic system representing symmetrical types, evidently this mode of approach will not be very helpful for the synthesis of the carbon framework having an unsymmetrically substituted ring-system. Hence an altogether different approach should be sought for. One published approach (III) in this direction is to piece together different units and is due to Halsall (Halsall et al, J. Chem. Soc., 1956, 2431; 1957, 3441) and another approach is to build



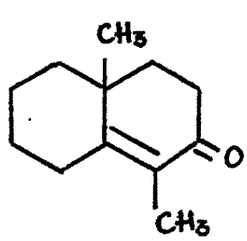
III

up the molecule ring by ring although the latter process may be extremely laborious and also involving complicated stereochemistry. Preliminary attempts were undertaken in this laboratory to utilise the last method (Sharma, D. Phil. Thesis, Calcutta University, 1960) in which a compound of the following structure (IV ?) has been described as an oil. Subsequent investigations have revealed that some of the intermediate

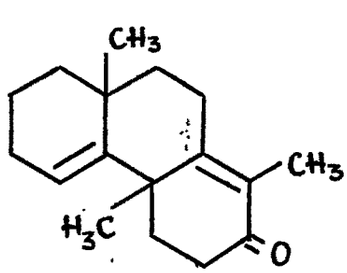


IV ?

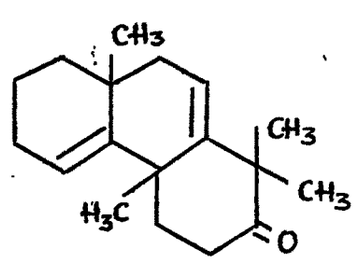
compounds described earlier contain extra methyl group or groups and these have evidently arisen during methylation with excess of potassium t-butoxide (Conia, Bull. Soc. Chim. France, 1954, 690, 943) although methylation was carried out under standard procedures. Moreover analytical values vary very insignificantly (ca. 0.2 %) with the introduction of an additional methyl group in the desired compound. So the entire plan of work has been fully re-examined and all the compounds have now been characterised by well-defined crystalline structures and other reactions. The scheme of work may be depicted below.



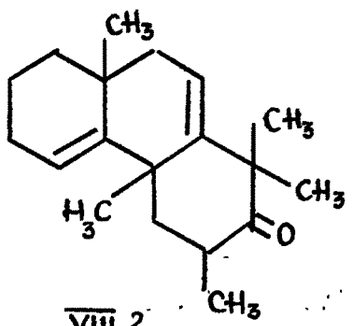
V



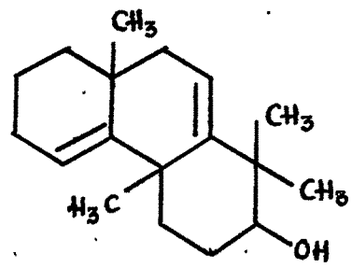
VI



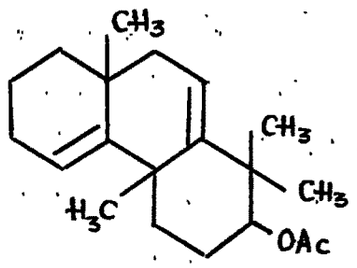
VII



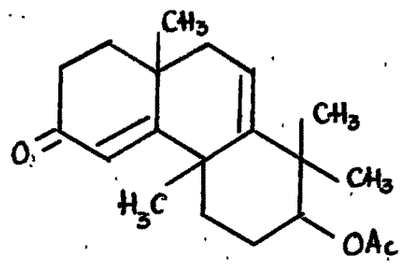
VIII ?



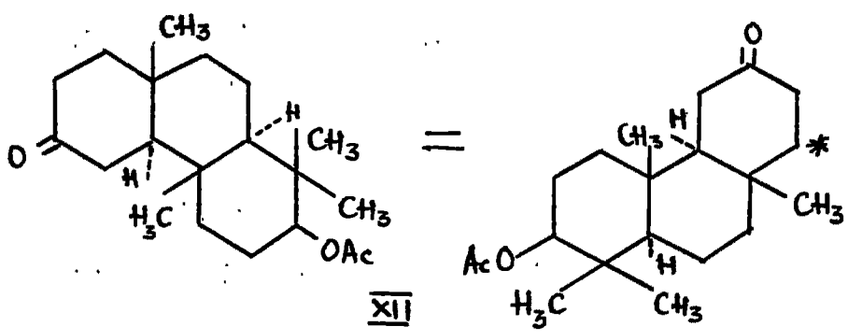
IX



X



XI



XII

The ketone (V) (Dutta et al, J. Chem. Soc., 1956, 4978) was condensed with β-chloroethyl ethyl ketone in presence of potassium t-butoxide and the condensation product on subsequent ring-closure with sodium methoxide in methanol afforded the unsaturated ketone (VI) as a well-defined crystalline solid and in a satisfactory yield. The process of subsequent methylation at ∝-position of the

$\alpha\beta$ -unsaturated ketone with methyliodide in presence of potassium t-amylate has been found to be highly critical. When 2 moles were used, the methylated product was found to be a highly crystalline solid, m.p. 111°, already reported by Sharma. This compound failed to react with ethyl formate indicating the absence of a reactive methylene group. Evidently this is an "overmethylated" product (VIII). The compound is spectroscopically transparent in the region 230-250 mμ. When 1.6 moles of potassium were used, the crystalline material also obtained in this operation, does not show any absorption in the ultra-violet in the region 230-250 mμ. The compound was however found to be an impure mixture from which the pure component (VII) could not be isolated in a satisfactory yield through crystallisation. When 1.3 moles of potassium were used, the expected compound (VII), m.p. 91°, could be isolated in a good yield from the crude reaction mixture. This readily condensed with ethyl formate in presence of sodium methoxide. This definitely shows that the compound, m.p. 111° contains additional methyl groups, the number of which cannot be determined either through analytical values or through titration with bromine due to the presence of unsaturation in the molecule. The doubly unsaturated ketone (VII)was reduced with sodium and alcohol in order to obtain the hydroxyl group in the desired equatorial position and the crystalline hydroxy-compound so obtained, was directly acetylated to afford (X) in a highly crystalline state. Attempt was next made to oxidise preferentially at the less hindered allylic position

with a view to obtaining (XI) and after a series of experiments the success could be achieved in a moderate yield by carrying out the reaction at 40°. The formation of the ketone was detected through ultra-violet absorption at 240 mμ. Although the ketone could not be obtained in an analytically pure condition, it has been readily characterised by an orange-red 2:4-dinitrophenylhydrazone, m.p. 205-206°. With a view to removing most of the unoxidised material (X), the product was treated with a small quantity of methanol and the filtered solution contained about 80 % of the oxidised material as revealed in the infra-red studies. This was directly hydrogenated over palladium-charcoal catalyst in alcohol to afford the saturated ketone (XII), characterised through the yellow 2:4-dinitrophenylhydrazone. It will be apparent from the steric course of the catalytic reduction that the saturated ketone (XII) will most probably have the stereochemistry as depicted here, because of the presence of so many axial methyl groups. As a result, all the asymmetric centres in (XII) have most likely the desired stereochemistry as is found in A, B and C rings of the pentacyclic triterpenoids. In order to push the synthetic scheme further, it is in view to introduce two substituents viz., "methyl" and "CH_2CH_2OH" at (*) in (XII) and for this purpose it will be helpful to develop unsaturation through bromination and to study conjugate addition of methyl-magnesium iodide and also Michael reaction with diethyl malonate. The investigation is in active progress.

EXPERIMENTAL

2-Keto-1,12,14-trimethyl-2,3,4,6,7,8,9,10,12,14-decahydrophenanthrene (VI).

Potassium (5.4 g.) was dissolved in excess of t-butyl alcohol and the latter was distilled off until a solid appeared in the flask. This was then cooled to the room-temperature and 1,10-dimethyl-2-keto-$\Delta^{1,9}$-octalin (22.5 g.) was added in one lot with shaking under nitrogen atmosphere, whereupon the mixture turned deep red in colour. Mixture was warmed on a water-bath (70-80°) for one hour. It was then cooled in a freezing mixture and β-chloroethyl ethyl ketone (20 g.) was added slowly with occasional shaking and this was left overnight. Finally it was refluxed for 3 hours, cooled, acidified with cold hydrochloric acid (6 N) and extracted with benzene. After removal of the solvent, the residue on distillation gave a forerun of the unreacted ketone (9.5 g.) and finally the desired product (15 g.), b.p. 140-180°/0.5 mm. This was refluxed with a methanolic solution of sodium methoxide prepared from sodium (4.2 g.) and dry methanol (145 c.c.), under nitrogen atmosphere for 6 hours. It was left overnight. The solution was cooled and just acidified with hydrochloric acid and methanol was removed. The residue was treated with water and extracted with ether. The ethereal solution was washed with a solution of sodium carbonate (5 %), water and dried over sodium sulphate. On removal of the

solvent and distillation a thick liquid (8.5 g.), b.p. 155-170°/0.4 mm. was obtained. This on treatment with petroleum ether (40-60°) in the cold, afforded a solid material (4.2 g.). It crystallised from the same solvent in white flakes, m.p. 83°. λ_{max}^{alc} 250 mμ, log ε 4.1.

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.5; H, 9.9.
Found : C, 83.3; H, 10.0.

It afforded a bright-red 2:4-dinitrophenylhydrazone, which crystallised from ethyl acetate in shining flakes, m.p. 224°.

2-Keto-1,1,12,14-tetramethyl-1,2,3,4,6,7,8,9,12,14-decahydrophenanthrene (VII).

To an ice-cold solution of dry potassium t-amylate (potassium 1.74 g.) in benzene (150 c.c.) was added dropwise the above tricyclic ketone (8.3 g.) in benzene (10 c.c.) with occasional shaking under nitrogen atmosphere. The reaction mixture was left at room-temperature for 2 hours and kept at 60-70° (bath-temperature) for one hour, when the colour of the solution turned chocolate brown. It was next cooled in a freezing mixture and after addition of methyl iodide (9 c.c.) it was left overnight. On refluxing finally for 2 hours, the milk-white reaction mixture was poured into ice-cold water and acidified with hydrochloric acid. The benzene layer was separated and the aqueous layer extracted with benzene. The

combined benzene layer was washed with sodium thiosulphate solution (5 %), water and dried over sodium sulphate. On removal of the solvent, the residue was treated with petroleum ether (40-60°), when crystals (4.5 g.) appeared. This was recrystallised from the same solvent, m.p. 91°.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.6; H, 10.1.
Found : C, 83.7; H, 10.2.

2-Acetoxy-1,1,12,14-tetramethyl-1,2,3,4,6,7,8,9,12,14-decahydrophenanthrene (X).

A warm solution of the above ketone (3.3 g.) in absolute ethanol (40 c.c.) was quickly added to sodium (3 g.). It was then heated until the whole of sodium went into solution (3 hours). On cooling to room-temperature, the product was diluted with water (ca. 300 c.c.), saturated with sodium chloride and extracted with ether. The ethereal extract was washed with water and dried over sodium sulphate. On removal of the solvent and keeping at room-temperature the hydroxy compound (3.1 g.) crystallised in shining needles, m.p. 113-114° (crude). To a thoroughly cooled solution of the hydroxy compound (3 g.) in pyridine (5.6 c.c.) was slowly added a mixture of acetic anhydride (4.3 c.c.) and acetyl chloride (2 c.c.), whereupon a white precipitate separated. Ether (20 c.c.) was then added and the reaction mixture left overnight at room-temperature. It was then poured on ice

containing concentrated hydrochloric acid and ether. The organic layer was separated and the aqueous layer was extracted with ether. The combined ethereal extract was washed successively with water, sodium bicarbonate solution (5 %), water and dried over sodium sulphate. On removal of the solvent, the residue (3 g.) which solidified, did not show any band for hydroxyl group in the infra-red. It crystallised from petroleum ether (40-60°) in transparent plates, m.p. 110-111°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0.
Found : C, 79.1; H, 10.2.

2-Acetoxy-1,1,12,14-tetramethyl-6-keto-1,2,3,4,6,7,8,9,12,14-decahydrophenanthrene (XI).

A solution of the acetoxy compound (3 g.) and sodium dichromate (3 g.) in glacial acetic acid (45 c.c.) was stirred for 14 hours at room-temperature and then heated at 40° (bath-temperature) with vigorous stirring for 3 hours. Ethanol (3 c.c.) was added to the hot solution to decompose the excess of dichromate and the resulting green solution was diluted with water, cooled and extracted with ether. The ethereal extract was thoroughly washed with cold sodium carbonate solution (5 %), water and dried over sodium sulphate. The residue obtained on removal of the solvent was triturated with methanol, whereby a solid separated out. It was then filtered and the solvent

was removed from the filtrate. The residue (1.7 g.) (λ_{max}^{alc} 240 mμ; log ε 3.8) exhibited also in the infra-red bands, for αβ-unsaturated ketone (6.01 μ) and the acetoxy-group (5.80 μ; 8 μ). It afforded an orange-red 2:4-dinitrophenylhydrazone, which crystallised from ethanol in small shining needles, m.p. 205-206°.

Anal. Calcd. for $C_{26}H_{32}O_6N_4$: C, 62.9; H, 6.5.
Found : C, 63.2; H, 6.9.

The solid left after filtration, as described above, crystallised from methanol in flakes, m.p. 110°, which showed no depression in m.p. on admixture with the acetoxy compound (X).

2-Acetoxy-1,1,12,14-tetramethyl-6-keto-perhydrophenanthrene (XII).

The crude residue (1.5 g.) left after removal of the unoxidised material as described in the preceding experiment, was taken in ethanol (25 c.c.) and shaken in an atmosphere of hydrogen over palladium-charcoal catalyst (0.2 g., 10 %). Absorption of the theoretical amount of hydrogen was complete on shaking overnight. There was no more absorption of hydrogen on addition of a further quantity of the catalyst (0.1 g.). After filtering, ethanol was removed from the filtrate and the residue (1.4 g.) did not show any characteristic absorption for the αβ -unsaturated carbonyl group in the ultra-violet. It readily afforded a bright-yellow 2:4-dinitrophenylhydrazone

(crude m.p. 233-234°), which on crystallisation from ethyl acetate-ethanol (3:1) yielded bright-yellow needles, m.p. 234-235°.

Anal. Calcd. for $C_{28}H_{36}O_6N_4$: C, 62.4; H, 7.2.
Found : C, 62.2; H, 7.1.