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DEVELOPMENT OF CONVERGENT TOTAL SYNTHESIS OF EQUILENANE AND ESTRANE MOLECULES

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SIR ROBERT ROBINSON,[1] in his numerous excurtions for the synthesis of steroids, once observed that a cyclopentanone derivative (1) with appropriate substitutions at 2 and 3 positions was likely to prove useful for the purpose. But no attempt to prepare such a compound was later reported.

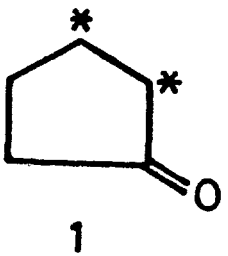

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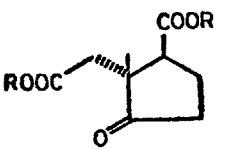
Chart I

Banerjee and Das Gupta[2] considered that 2-methyl-3-carboxycyclopentanone-2-acetic acid (2) with the required steric configuration would prove to be an ideal synthone for a convergent total synthesis of aromatic steroid molecules.



2a, R=H
b, R= C_2H_5

Chart II

Chakravarty and Banerjee[3] had studied the cyclization of ethyl 2-methyl-2-carbethoxypimelate (3) with sodium in benzene, with could give rise to two

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cyclohexanone β-keto esters (4 and 5) and/or the cyclopentanone β-keto ester (6). However, the cyclized product on hydrolysis and decarboxylation yielded a single crystalline product. It may be observed that the aforementioned treatment of 4 and 5 should form only one product, *viz* 3-methyl-3-carboxycyclohexanone (7), whereas cyclopentanone-2-methyl-2-acetic acid (8a) would result from 6. We prepared authentic specimens of 7 and 8a by unambigous methods and showed by direct comparison that the cyclopentanone derivative (6) was the only product of cyclization of the triester (3).

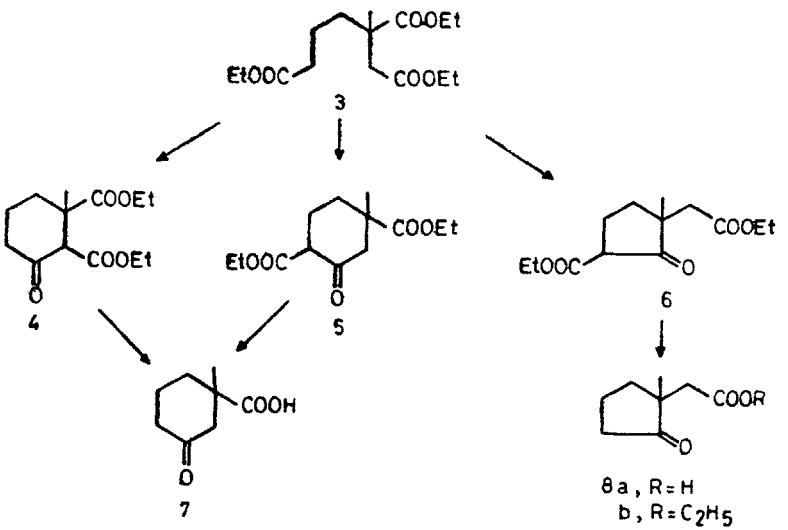


Chart III

Encouraged by the result of the above cyclization study, Banerjee and Das Gupta[2] decided to cyclize ethyl 2-methyl, 3-dicarbethoxypimelate (12) under the same condition with the hope of obtaining 2. For the preparation of 12, ethyl α-acetoglutarate (9) was condensed with ethyl cyanoacetate to obtain the unsaturated cyanoester (10). Addition of hydrogen cyanide to 10 afforded the dicyanoester (11), hydrolysis, decarboxylation and esterification of which furnished the required tetraester (12).

The possibility of formation of two cyclohexane β-keto esters (13 and 14) and one cyclopentane β-keto ester (15) was also there in the cyclization of 12. Hydrolysis and decarboxylation of the cyclized product in this case also gave one crystalline product, a keto dibasic acid.

The above keto dibasic acid on treatment with acetic anhydride gave an anhydride (18), from which the regenerated acid (19) was found to be different from the starting keto dibasic acid. Semicarbazones of diethyl esters of both 17 and 19 were different from the semicarbazone of the diethyl ester of the cyclohexane

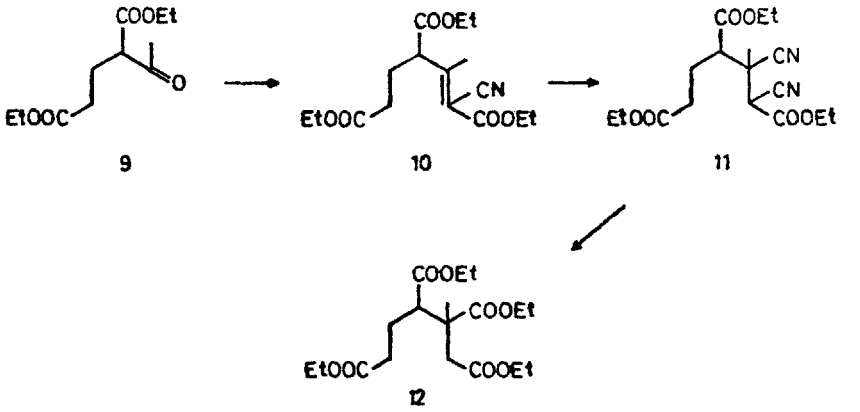


Chart IV

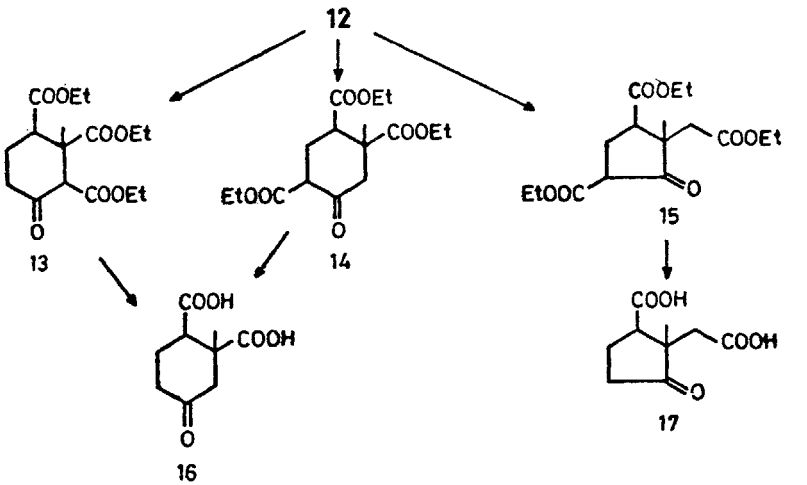


Chart V

keto dibasic acid (16), earlier prepared by Mukharji.[4] The above experiments showed that cyclization of 12 followed by hydrolysis and decarboxylation led to the formation of a cyclopentanone diacid which had the steric configuration of our desired product (2a).

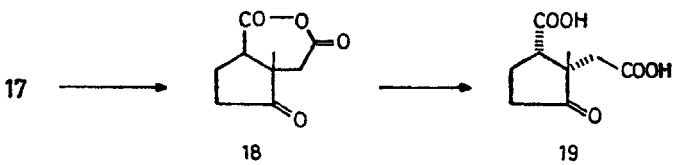
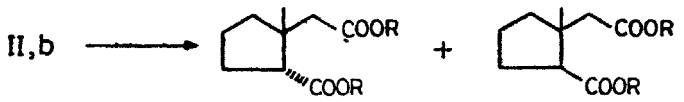


Chart VI

To provide further confirmation of the structure of 2, the keto diester (2b) was reduced with zinc amalgam and refluxing alcoholic hydrogen chloride to obtain a stereoisomeric mixture of the diesters (20c and 21c), the acid hydrolysis of which gave mixture of the stereoisomeric diacids (20a and 20b) which could be separated by crystallization into the known *trans*- and *cis*-acids, 20a and 21a respectively. Obviously, treatment of the sterically homogeneous 2b with alcoholic hydrogen chloride during the reduction experiment was responsible for the isomerization.



20 21

a, R=H
b, R=CH_3
c, R=C_2H_5

Chart VII

Banerjee and Das Gupta[3] also prepared authentic specimens of 20a and 21a by an independent method for direct comparison. The keto ester (8b) was converted into the unsaturated nitrile (23), *via* the cyanohydrin (22), which was saponified and esterified to afford the unsaturated ester (24), hydrogenation of which gave a mixture of 20b and 21b. Acid hydrolysis of the above mixture followed by treatment with acetic anhydride furnished the anhydride (25), from which the pure *cis*-acid (21a) was obtained. Equilibration of the *cis*-ester (21b) by treatment with potassium *t*-butoxide, followed by saponification and fractional crystallization furnished the *trans*-acid (20a).

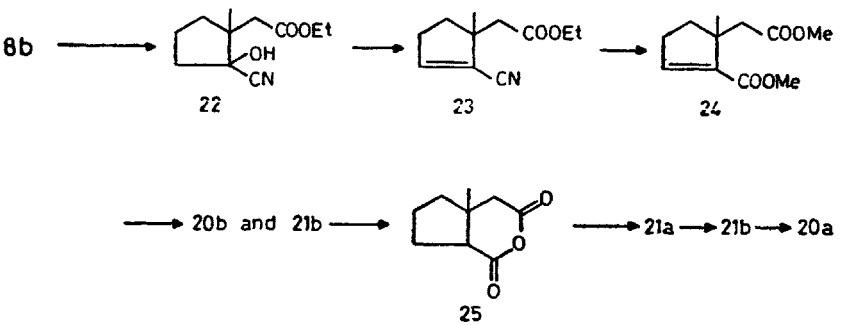


Chart VIII

For the convergent formation of the equilenane molecule, Banerjee *et al.*[5] condensed 2-methoxy-6-lithionaphthalene (26), prepared from 2-methoxy-6-bromonaphthalene, with the dimethyl ester (27) of 2a and the resulting condensation product was dehydrated and saponified to obtain 3-methyl-4-carboxy-2-(2'-methoxy-6'-

naphthyl) cyclopenten-3-acetic acid (28a) in 25 per cent yield. The point of attachment of the cyclopentane ring to the naphthalene nucleus was proved by oxidizing 28b to 2-methoxy-6-naphthoic acid (29). With recent improvements in the lithiation experiments, there is considerable scope for improvement in the condensation stop.

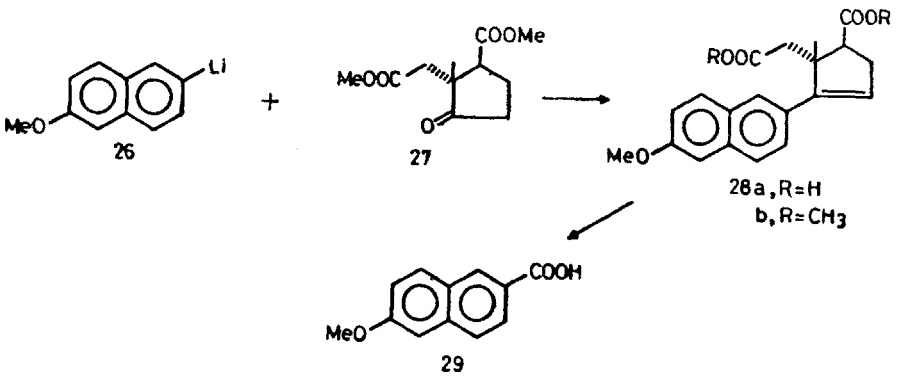


Chart IX

The synthesis was tried under three different conditions *viz.* the treatment of the acid chloride of 28a with aluminium chloride, that of 28a or 28b with PPA and that of a solution of 28a in phosphorous oxychloride with PPA for the ring closure to obtain the equilenane unsaturated keto acid (30), the last one giving the best yield (73 per cent). Hydrogenation of 30 with Raney nickel gave the saturated keto acid (31) in 70 per cent yield, whereas use of 5 per cent Pd-C and stopping the hydrogenation after the absorption of one mole of hydrogen raised the yield to 83 per cent. Hydrogenation with 30 per cent Pd-C, until the absorption stopped, furnished 3-methoxyequilenane-

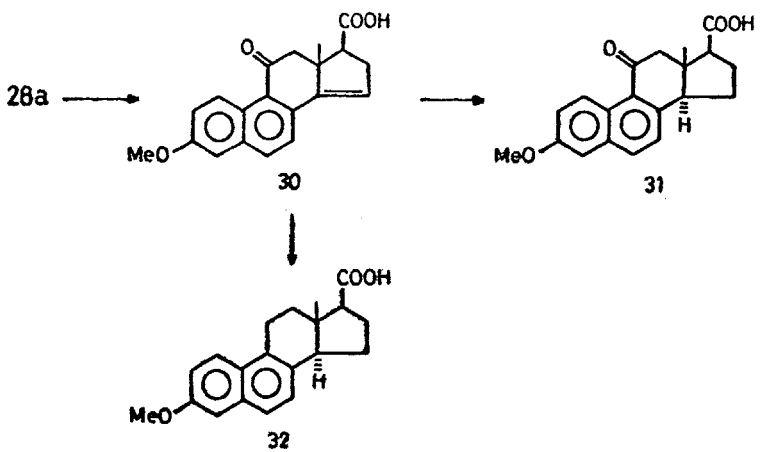


Chart X

17β-carboxylic acid (3-methoxy-17β-carbpxy-1,3,5(10),6,8-estraoentane) (32). Banerjee *et al.*[6] had earlier prepared 32 by a longer route and provided rigorous proof for its structure and configuration. The two products were shown to be identical by direct comparison.

It may be noted that from starting with the preparation of the synthone (2) to its three step convergent conversion to the equilenane (32), the whole process is entirely stereospecific.

Banerjee *et al.*[7] completed the convergent synthesis of the estrane molecule (35) from 2 by the streospecific conversion of the equilenane keto acid (31) to 35. The conversion of an equilenane molecule, *viz.* 17β-dihydroequilenin, to an estrane, *viz.* 17β-estradiol, was claimed by Marker,[8] but it could not be substantiated.

The metal-amine reduction of 31 gave 3-methoxy-17β-carboxy-1,3,5(10),8-estratetraene (33) in good yield. Comparison of δ values of 1- and 6-protons in the PMR sprectra of 31 and 33 provided excellent proof in favour of the structure of 33. The doublet (J10) at δ 9.33 due to the C-1 proton of 31 is more deshielded by the 11-keto group than the doublet (J10) at δ 8 of the same proton of 33 because of the difference in distances, 1.55 and 1.66Å (Dreiding model) respectively, and the doublet at δ 7.9 (J10) due to the C-6 proton in 31, deshielded by the 11-keto group in the para position, disappears because of the loss of aromaticity of the B-ring in 33. Clemmensen reduction of 33 furnished 1,3,5(10),9(11)-estratetraene (34). The absenee of the carbonyl group in the IR and the presence of vinyl proton in the PMR proved its structure and the shift of the 8(9) double bond to 9(11) proved the *trans*-configuration of the CD-ring. Catalytic hydrogenation of 34 gave 3-methoxy-17β-carboxy-1,3,5(10)-estratriene (35). This happens to be one of the first successful conversion of an equilenane to the estrane molecule. Instead

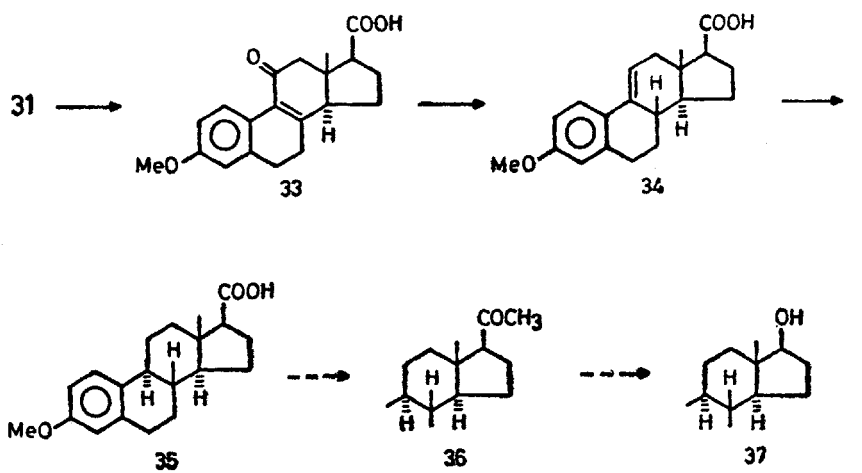


Chart XI

of proving the structure and configuration of 35 by its conversion to *dl*-estradiol methyl ether (37) through the routine steps consisting of the preparation of the ketone (36) followed by its Bayer-Villiger oxidation, we proved it as follows.

The cyanohydrin (39) of *dl*-estrone methyl ether (38) was dehydrated to the unsaturated nitrile (40) which on successive treatment with potassium hydroxide and dimethyl sulphate afforded the unsaturated acid (41). Catalytic hydrogenation of 41 furnished the authentic specimen of 35 which was found to be identical in all respect by direct comparison with the compound (35) prepared from 31.

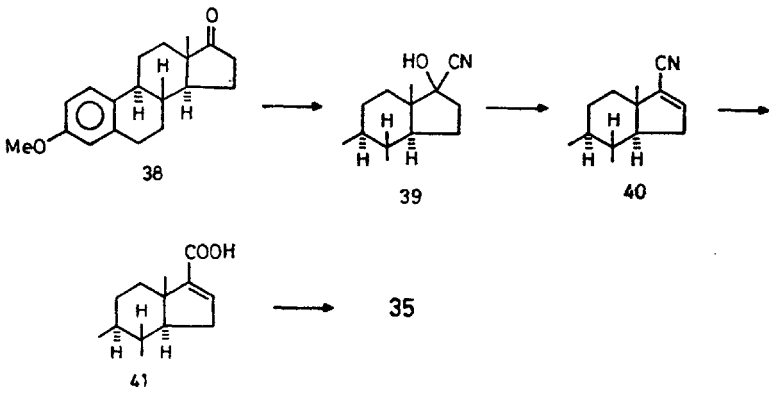


Chart XII

Simultaneously with our publication, a nonstereospecific conversion of 3-methoxy-11-17-diketo-1,3,5(10),6,8-estrapentaene, an equilenane, to *dl*-estrone methyl ether was reported.[9]

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