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SYNTHESIS OF CYANOMACLURIN—I

SYNTHESIS OF SOME MODEL COMPOUNDS

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Abstract—Based on NMR evidence cyanomaclurin is considered to have a chromanochroman (cyanomacluran) skeleton. In order to provide synthetic support three model compounds without the 13-hydroxyl group have been prepared. These are 3-methoxy, 1,3-dimethoxy and 3,9-dimethoxy cyanomaclurans made from corresponding 2′-hydroxy flavanones. Their properties and the readiness with which the final chroman ring closure takes place, support the structure of cyanomaclurin.

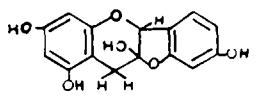
CYANOMACLURIN, the water soluble colourless component of the heart-wood of *Artocarpus integrifolia* (Jack wood) was originally assigned[1] the chromano-coumaran structure (I) based on its composition, chemical properties and reactions. In view of the similarity of the compound with ordinary leucoanthocyanidins which are 3,4-diols, the NMR spectrum of the trimethyl ether was examined to see if a methylene group existed in 4-position. It gave definite evidence for its absence. Therefore, formula II was suggested by Chakrabarty and Seshadri.[2] They also noted that the normally expected reactions of benzyl alcohol group, —CHOH, particularly oxidation with activated manganese dioxide did not proceed. But they explained this feature as due to the interference of the neighbouring oxygen substitutions because in leucoanthocyanidins of the leucopelargonidin group this difficulty exists. The lack of oxidation could also be due to another cause; based on a comparison of the NMR signals for cyanomaclurin and its acetate, Nair and Venkataraman[3] suggested the chromanochroman formula (III) in which the 4-hydroxyl is involved in ring formation. This formula was also supported by the readings of the NMR spectra[2] of the trimethyl ether of cyanomaclurin and its acetate which had a similar relationship and structure (III), therefore, explains all the properties of cyanomaclurin. Interpretation of such NMR data should be taken with caution specially in the absence of detailed study of related model compounds. Moreover, structure III is an entirely new type of oxygen heterocycle and is probably the only known member of this class. In order to provide a better understanding of physico-chemical data pertaining to the skeleton of III, some model compounds of this type were synthesized, the ultimate aim being a final synthetic proof of the structure of cyanomaclurin. In this paper we report the synthesis of three such models possessing the chromano-chroman skeleton but lacking the secondary alcoholic hydroxyl group of the natural compound. As these compounds possess a new type of skeleton and more may be encountered among natural and synthetic products, the numbering of positions is indicated in IV and the name cyanomacluran is proposed for this skeleton.

* This paper is dedicated to the memory of Professor H. Stephen.

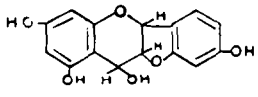
[1] H. Appel and R. Robinson, *J. Chem. Soc.* 752 (1935).

[2] G. Chakrabarty and T. R. Seshadri, *Tetrahedron Letters* No **18**, 787 (1962); *Curr. Sci.* **32**, 251 (1963).

[3] P. M. Nair and K. Venkataraman, *Tetrahedron Letters* No **5**, 317, (1963).



I



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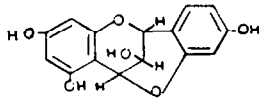
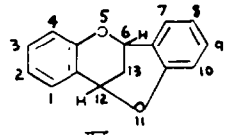


III

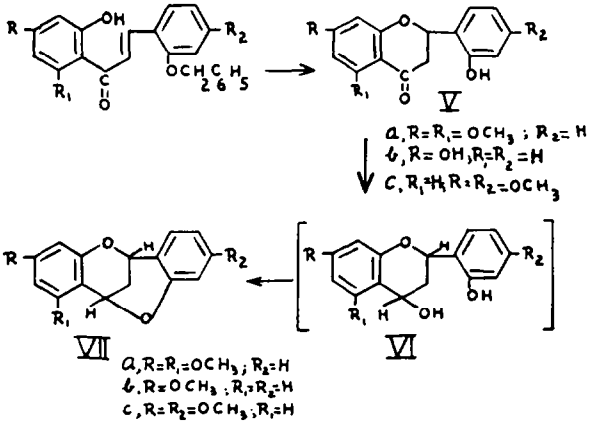


IV

The principle followed in these syntheses is based on that adopted for the chromanocoumarans like homopterocarpin[4] and related compounds.[5] It involves reduction of a 2′-hydroxyflavanone and cyclization of the resulting flavan-4-ol under mildly acidic conditions. The starting 2′-hydroxyflavanones are difficult to prepare but by using special methods moderate yields are obtained.

The first model compound, 1,3-dimethoxy cyanomacluran (VIIa), required 2′-hydroxyflavanone (Va) which was reduced; the resulting flavan-4-ol was not isolated but directly cyclized by acidification with acetic acid. Subsequent repetitions showed that cyclization takes place spontaneously to some extent during reductions but the yields are low; acid treatment is necessary for completion of the reaction.

The second model (VIIb) was chosen in order to study whether the absence of a 5-methoxyl group in the flavanone has any effect on this type of cyclization. Initial attempts to obtain the required 7-methoxy-2′-benzyloxy or 7-methoxy-2′-hydroxyflavanones by ring closure of the corresponding chalkones under a variety of acidic conditions were not successful. But 2′-benzyloxy-7-hydroxyflavanone could be obtained from the dihydroxychalkone under alkaline conditions. Methylation of this gave an uncrystallizable oil which on catalytic debenzylation yielded the required 2′-hydroxyflavanone. Reduction, as in the previous case, gave flavan-4-ol which



[4] K. Aghoramurthy, A. S. Kukla and T. R. Seshadri, *Curr. Sci.* **30**, 218, 1961; *J. Indian Chem. Soc.* **38**, 914 (1961).

[5] H. Suginome and T. Iwadari, *Bull. Chem. Soc. Japan* **33**, 567 (1960); *Experimental* **15**, (IV),163 (1962).

needed stronger acidic conditions e.g. dil. hydrochloric acid, to undergo cyclization to the neutral cyanomacluran (VIIb).

In the third case (VIIc), the catalytic debenzylation of 7,4′-dimethoxy-2′-benzyloxyflavanone did not yield a pure product. TLC showed the absence of starting substance, the major spot being due to the 2′-hydroxyflavanone (Vc) followed closely by a minor spot probably due to the flavan-4-ol (VI, $R_1 = H$; $R = R_2 = OCH_3$) produced by further reduction. As the mixture proved difficult to separate, it was reduced with sodium boro-hydride and subsequent cyclization with dil. hydrochloric acid gave the desired VIIc.

Discussion of spectral data

Since the above skeletons are new it was desirable to record physical data for comparison with cyanomaclurin; compound VIIa, being available in larger amount, was subjected to a thorough UV, IR, NMR and mass spectral investigation whereas the others were used for UV and IR only.

In UV all the three model compounds showed maxima near about 280 mμ as is also reported for cyanomaclurin trimethyl ether; moreover the curves are exactly parallel to that of the methyl ether of the natural compound. However, with increasing substitution of methoxyl groups the intensity of the peak (log ε) decreases.

The IR spectra of these compounds do not reveal any peak (band) characteristic of the skeleton but a few maxima are common to all of them.

NMR spectra of VIIa shows general similarity to that of the trimethyl ether of cyanomaclurin. In particular the benzylic protons at C_8 and C_{12} are centered at 5·70 and 5·30 ppm. The two methoxyl groups appear as two different singlets at 3·75 ppm and 3·85 ppm. A doublet with *meta* coupling can be observed at 6 ppm

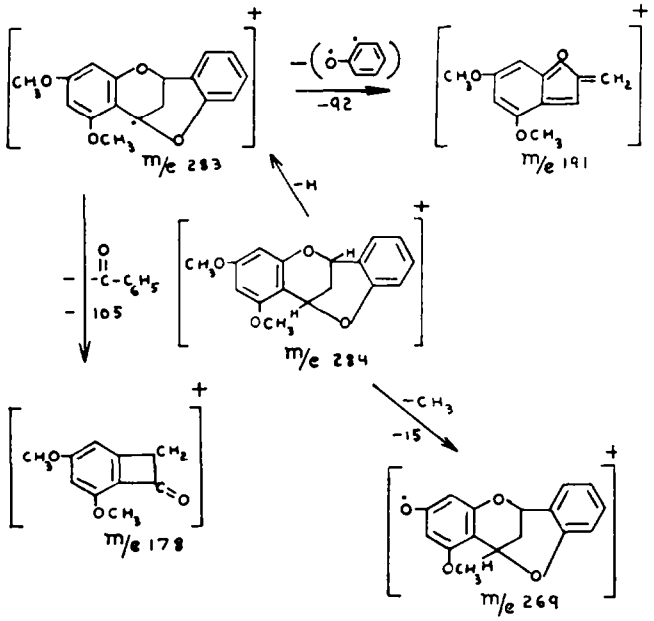


CHART I

corresponding to the protons at positions C_2 and C_4. The two protons at position 13 give a slightly split triplet centered at 2·20 ppm.

The mass spectrum of 1,3-dimethoxycyanomacluran (VIIa) revealed five major peaks, *m/e* 284, 283, 269, 191 and 178. The relative abundance of these peaks are 100, 35, 19, 21 and 40 percent respectively and these presumably arise by the fragmentation process shown in Chart I and lend support to the structure VIIa. The stability of the skeleton is revealed by the fact that the molecular ion (*m/e* 284) also forms the base peak.

EXPERIMENTAL

2-Benzyloxy-2',4'-dihydroxychalkone

A solution of resacetophenone (2 g) and *o*-benzyloxybenzaldehyde (2·8 g) in alcohol (20 ml) was mixed with KOH (15 g) in water (10 ml). The dark red mixture was kept at room temp for 48 hr with occasional shaking, then diluted with water (100 ml) and extracted with ether (2 × 50 ml) to remove the unreacted aldehyde. The red semi-solid which separated on acidification of the cooled alkaline solution, was extracted with ACOEt (2 × 75 ml). The dried extract on concentration and treatment with pet. ether yielded the chalkone (1·5 g) as the first crop. Further dilution of the mother liquors yielded some unchanged resacetophenone. The chalkone crystallized from MeOH as yellow needles, m.p. 186°. (Found: C, 75·8; H, 5·4. $C_{22}H_{18}O_4$ requires: C, 76·3; H, 5·2%.)

2'-Benzyloxy-7-hydroxyflavanone (A)

A mixture of the chalkone (2 g) in alcohol (75 ml) with NaOH (1·5 g) in water (75 ml) was refluxed for 30 min under N_2. After keeping it at room temp for 24 h most of the alcohol was removed under red. press. and the residue diluted with water (100 ml), cooled and acidified with HClaq. The precipitated light yellow solid was dried and mascerated with ACOEt (5 ml) and filtered. The residue was crystallized twice from benzene when it gave colourless needles of the flavanone (400 mg), m.p. 164°. (Found: C, 75·8; H, 5·6. $C_{22}H_{18}O_4$ requires: C, 76·3; H, 5·2%.)

2'-Hydroxy-7-methoxyflavanone

2'-Benzyloxy-7-methoxyflavanone was obtained as a viscous oil from A (500 mg) by heating under reflux for 1 hr with dimethyl sulphate (0·14 ml) and anhydrous K_2CO_3 (1·5 g) in acetone solution. Methylation with excess of diazomethane also gave the same product. This benzyl ether (400 mg) in ACOEt (100 ml) containing a few drops of triethylamine was shaken with Pd–C (5%; 100 mg) in an atmosphere of H_2. Absorption (15 ml) of H_2 was complete in 0·5 hr. The colourless product (300 mg) obtained after evaporation of the filtered solution, crystallized from MeOH as needles, m.p. 193–194°. (Found: C, 71·0; H, 5·5. $C_{16}H_{14}O_4$ requires: C, 71·1; H, 5·2%.)

3-*Methoxycyanomacluran* (VIIb)

Sodium borohydride reduction of 2'-hydroxy-7-methoxyflavanone. A solution of the above flavanone (100 mg) in alcohol (12 ml; 80%) and boric acid (300 mg) was treated dropwise with $NaBH_4$aq (3 ml, 5%). After keeping for 3 hr at room temp, the mixture was diluted with water (100 ml) and acidified with very dil HClaq. The faintly turbid solution was extracted with ether 3(× 50 ml) and the concentrated extract washed successively with NaOHaq (3 × 6 ml; 1%) and saturated brine. After drying, the solution was distilled off when a white solid was obtained which crystallized from alcohol as colourless glistening plates m.p. 99–100°. (Found: C, 75·2; H, 5·5. $C_{16}H_{14}O_3$ requires: C, 75·6; H, 5·6%.) Light absorption data: ν_{nujol}^{max} 1615, 1560, 1250, 1200, 1150, 1125 cm^{-1}, λ_{EtOH}^{max} 280 mμ (log ε 3·19) and an inflexion at 320 mμ.

1,3-*Dimethoxycyanomacluran* (VIIa)

Sodium borohydride reduction of 2'-hydroxy-5,7-dimethoxyflavanone. The flavanone (Va; 250 mg) was reduced by adding gradually $NaBH_4$aq (3 ml, 2·5%) to a vigorously shaken solution in alcohol (20 ml) containing boric acid (200 mg). After 3 hr at room temp, the solution was diluted and acidified with dil ACOH. Extraction with ether, washing the extract with $NaHCO_3$aq and sat. brine and evaporation yielded a gum (150 mg) which solidified on masceration with a little alcohol. It

crystallized from alcohol as colourless prisms, m.p. 111–112°. (Found: C, 71·3; H, 6·2. $C_{17}H_{16}O_4$ requires: C, 71·8; H, 5·7%.) The IR showed bands at ν_{KBr}^{max} 1616, 1283, 1200, 1137, 1100, 990 cm^{-1} and in UV it absorbed at λ_{EtOH}^{max} 275 mμ (log ε 2·67).

2-Benzyloxy-4-methoxy-2',4'-dihydroxychalkone

Aqueous KOH (6 gm, in 6 ml) was mixed with a solution of resacetophenone (2 g) and 2-benzyloxy-4-methoxybenzaldehyde (3 g) in alcohol (45 ml). The mixture was covered with a layer of pet. ether and kept at room temp for 6 days. It was then diluted with water (100 ml) and extracted with ether to remove unchanged aldehyde. The dark red solid obtained on acidification of the cooled alkaline solution was filtered, dried and mascerated with AcOEt (10 ml) and the insoluble orange yellow chalkone (1·5 g) filtered off. It crystallized from MeOH as yellow needles, m.p. 201–202° and gave a deep brown colour with alcoholic $FeCl_3$. (Found: C, 73·3; H, 5·6. $C_{23}H_{20}O_5$ requires: C, 73·4; H, 5·4%.)

The AcOEt filtrate on dilution with pet. ether afforded a small amount (100 mg) of the corresponding flavanone described below.

2'-Benzyloxy-4'-methoxy-7-hydroxyflavanone

A mixture of the chalkone (1 g) in alcohol (50 ml) and NaOH (1 g) in water (50 ml) was refluxed for 30 min under inert atmosphere. After 12 hr at room temp, most of the alcohol was removed under red. press. and the diluted solution acidified. The resulting yellow solid was fractionally crystallized from AcOEt–pet. ether when the unchanged chalkone (500 mg) was obtained first and the slightly impure flavanone (250 mg) next. Recrystallization of the flavanone from MeOH afforded light yellow needles (200 mg) m.p. 171–172°. (Found: C, 70·6; H, 6·0. $C_{23}H_{20}O_5$, H_2O requires: C, 70·5; H, 5·5%.) It gave a blue colour with Mg and HCl.

2'-Benzyloxy-4'-7-dimethoxyflavanone (B)

Methylation of the flavanone (1 g) with dimethyl sulphate (0·27 ml) and K_2CO_3 (3 g) in acetone (100 ml) afforded the methoxyflavanone (700 mg). It crystallized from AcOEt as colourless needles, m.p. 160–161°. (Found: C, 73·4; H, 6·1. $C_{24}H_{22}O_5$ requires: C, 73·8; H, 5·7%.)

2'-Hydroxy-4'-7-dimethoxyflavanone

Catalytic debenzylation of B (500 mg) in AcOEt (150 ml) containing a few drops of triethylamine and Pd–C (250 mg; 10%) was complete in 1 hr. The product (340 mg) crystallized from MeOH as light yellow prisms m.p. 150° with earlier sintering. TLC over silica gel G showed it to be a mixture of two products (a) major spot due to the hydroxyflavanone (b) minor spot due to the corresponding 4-hydroxyflavan. As the mixture could not be purified without loss, it was reduced directly.

3,9-*Dimethoxycyanomacluran* (VIIc)

Sodium borohydride reduction of 2'-hydroxy-4',7-dimethoxyflavanone. The flavanone (100 mg) was reduced in alcohol (15 ml; 80%) containing boric acid (100 mg) with $NaBH_4$ (150 mg) in water (3 ml). The product obtained after 3 hr on acidification with dil. HClaq, crystallized from alcohol as colourless glistening plates (50 mg), m.p. 162–163°. (Found: C, 71·5; H, 5·9; $C_{17}H_{16}O_4$ requires: C, 71·8; H, 5·7%.) Its IR spectrum showed bands at ν_{nujol}^{max} 1616, 1260, 1180, 1150, 1120, 1040 cm^{-1} and in UV it absorbed at λ_{EtOH}^{max} 282 mμ (log ε 3·03).

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