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Biologically Active Carissone Derivatives*

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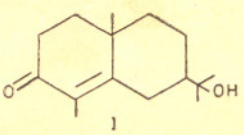
A series of substituted hydrazones, carbohydrazone, thiocarbohydrazones, carbazate, etc., derived from carissone, α-cyperone and 4,5-dihydrocarissamine, and 4H,5-cyanocarissone have been synthesized. The structure of 4H,5-cyanocarissone has been arrived at through its IR and UV spectral data. Carissone-3-(o-carboxyphenyl)hydrazone, 3,3′-bis-(carissyl) thiocarbohydrazone and carissone-3-N′-homopiperidyl hydrazone exhibit antizygotic, antimycobacterial and atropine-like spasmolytic activity respectively.

THE availability of carissone (I) in good yields from the roots of *Carissa carandas* Linn.[1] prompted us to convert it into biologically active derivatives. A series of substituted hydrazones, carbohydrazone, thiocarbohydrazones, carbazate, etc., derived from carissone, α-cyperone have been synthesized. The compound obtained by refluxing carissone with KCN and ammonium carbonate is shown to be 4H, 5-cyano-carissone, instead of the expected spirohydantoin derivative. Structural studies carried out on this compound are also reported in this communication.

Carissone oxime (m.p. 153-4°) prepared by the usual procedure was reduced over Raney nickel at 900 lb./sq. inch to give 4,5-dihydrocarissamine (II), which was converted into its hydrochloride, m.p. 307° (decomp.) (Found: C, 63·68; H, 10·45; N, 4·50. $C_{15}H_{29}NO.HCl.\frac{1}{2}H_2O$ requires C, 63·26; H, 10·89; N, 4·91%).



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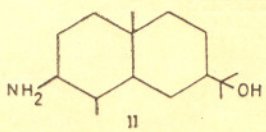

II

Attempt to prepare the 5-carboxymethylthiazolidine-4-one[2] derivative by refluxing carissone thiosemicarbazone and maleic anhydride failed to give the desired product.

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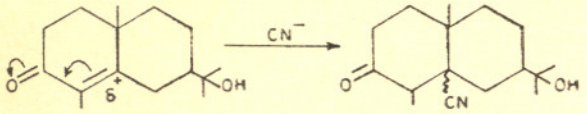
Carissone on being refluxed with KCN and ammonium carbonate in isopropanol did not yield the expected spirohydantoin derivative. Instead, a crystalline compound, m.p. 182-3°, analysing for $C_{16}H_{25}NO_2$ was obtained. The IR spectrum of this compound revealed a sharp peak at 2200 cm.$^{-1}$ ($-C\equiv N$) apart from the usual peaks as shown by carissone itself. However, the $>C=O$ peak was found to be at 1700 cm.$^{-1}$ as compared to 1650 cm.$^{-1}$ for carissone. The UV spectrum of carissone gave a maxima at 252 mμ whereas this compound did not show any such maxima. The shift of the carbonyl peak in the IR spectrum by 50 cm.$^{-1}$ and the absence of 252 mμ absorption in the UV spectrum indicated that the new compound was devoid of α,β-unsaturation. Based on these considerations this compound is to be considered as 4H, 5-cyanocarissone (III) (Found: C, 72·75; H, 9·91; N, 5·36. $C_{16}H_{25}NO_2$ requires C, 73·00; H, 9·50; N, 5·36%); $[\alpha]_D^{34}$ +25°. On theoretical considerations also, the cyano group would be expected to enter position-5.



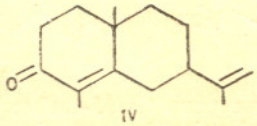
III

Refluxing equimolar mixture of carissone and the various substituted hydrazines, β-hydroxyethyl carbazate in ethanol or isopropanol furnished the corresponding hydrazones which are listed in Table 1. Carissone (2 moles) and carbohydrazide or thiocarbohydrazide (1 mole) under similar reaction conditions gave 3,3′-bis-carissyl carbohydrazone; m.p. 242°C. (Found: C, 70·80; H, 9·83; N, 10·54. $C_{31}H_{50}N_4O_3$ requires C, 70·72; H, 9·50; N, 10·64%); and 3,3′-bis-carissylthiocarbohydrazone; m.p. 244°C. (d) (Found: N, 10·50. $C_{31}H_{50}N_4O_2S$ requires N, 10·33%) respectively. Equimolar quantities of carissone and thiocarbohydrazide under similar conditions furnished carissone-3-monothiocarbohydrazone; m.p. 227°C. (Found: N, 17·72. $C_{16}H_{28}N_4OS$ requires N, 17·28%).

Carissone 3-(*o*-carboxyphenyl) hydrazone [Sl No. 7; R_f = 0·37 (chloroform)] was converted into its methyl ester [Sl No. 8; R_f = 0·5 (benzene)] by reacting it with diazomethane. The resulting compound on refluxing with hydrazine hydrate (80 per cent) in ethanol yielded the corresponding hydrazide (Sl No. 9).

Attempts to cyclize carissone-3-(*o*-carboxy and carbomethoxyphenyl) hydrazones (thermal or base-catalysed) were unsuccessful.

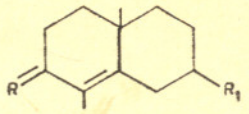
α-Cyperone (IV), obtained by heating carissone with $POCl_3$ in pyridine[3] (1 : 5) on a steam-bath for 1 hr and purified by distillation under reduced pressure (b.p. 145-60°/11 mm., $\lambda_{max.}^{EtOH}$ 249 mμ), was



IV

likewise converted into the corresponding hydrazones (Table 1).

TABLE 1 — HYDRAZONES, CARBOHYDRAZONES, THIOCARBOHYDRAZONES, CARBAZATE, ETC., DERIVED FROM CARISSONE, α-CYPERONE AND 4,5-DIHYDROCARISSAMINE



Sl No.	R	m.p. °C.	Mol. formula	N (%) Reqd	N (%) Found
	$R_1 = -C(CH_3)_2OH$				
1	-N-N< piperidyl	91	$C_{20}H_{34}N_2O$	8·80	9·07
2	-N-N< homopiperidyl	57-58	$C_{21}H_{36}N_2O$	8·43	9·10
3	-N-NHCO-pyridine(*p*)	179-80	$C_{20}H_{29}N_3O_2$	12·24	12·15
4	-N.NH. $COO(CH_2)_2OH$	110	$C_{18}H_{30}N_2O_4$*	7·83	7·94
5	N-NH<quinazoline(4)	130-31	$C_{23}H_{30}N_4O$	14·81	14·68
6	-N-NH. $C_6H_4F(p)$	152	$C_{21}H_{29}N_2FO$	8·13	7·87
7	$-N-NHC_6H_4$ $COOH(o)$	219-20	$C_{22}H_{30}N_2O_3$	7·56	7·45
8	$-N-NH.C_6H_4$. $COOMe(o)$	125-6	$C_{23}H_{32}N_2O_3$†	7·29	7·9
9	$-N.NH.C_6H_4$. $CO.NH.NH_2(o)$	170-71	$C_{22}H_{32}N_4O_2$	14·58	14·88
	$R_1 = -C(CH_3) = CH_2$				
10	N-NH<quinazoline(4)	158-60	$C_{23}H_{28}N_4$†	15·18	15·20
11	$-N-NH.C_6H_4$. $COOH(o)$	235 (decomp.)	$C_{22}H_{28}N_2O_2$	7·95	8·18
12	$-N.NH.C_6H_4$. $COOMe(o)$	90-92	$C_{23}H_{30}N_2O_2$	7·65	8·00

*Crystallized as monohydrate.
†Crystallized as hemihydrate.
Satisfactory C,H analyses were obtained for all the compounds.

Amongst the various compounds synthesized, carissone 3-(*o*-carboxyphenyl) hydrazone showed antizygotic activity at 50 mg./kg. level in mice and 3,3′-biscarissylthiocarbohydrazone showed significant antimycobacterial activity *in vitro* (1 : 250,000) (Bhaduri *et al.*, unpublished data). The LD_{50} of the latter was found to be 1 g./kg. in rats. Carissone-3-N′-homopiperidyl hydrazone exhibited atropine-like spasmolytic activity (200 mg./kg.).

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