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SYNTHESIS OF ROBUSTONE, ISOROBUSTONE, AND 4′-*O*-METHYLALPINUMISOFLAVONE: DECARBOXYLATIVE REARRANGEMENT OF ANGULAR ISOFLAVONE CARBOXYLIC ACIDS[1]

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ABSTRACT.—Phenacyl chromans **1–5** on reaction with ethoxalyl chloride in pyridine gave the esters **6**, **7**, **10**, and **14–16**, which were hydrolyzed to the acids **8**, **9**, **11**, and **17–19**. Decarboxylation of **8**, **9**, and **11** gave the dihydropyranoisoflavones **25**, **12**, and **13**. Demethylation of **13** gave **12**. However, the acids **17–19** on decarboxylation did not give the expected dihydropyranoisoflavones **20–22**; instead they yielded products identical with the linear dihydropyranoisoflavones **23–25**. Dehydrogenation of **24**, **25**, and **12** with DDQ gave 4′-*O*-methylalpinum isoflavone [**27**], robustone [**28**], and isorobustone [**29**], respectively.

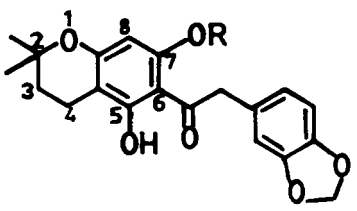
Robustone [**28**] and 4′-*O*-methylalpinum isoflavone [**27**] are linear pyranoisoflavones isolated from *Derris robusta* (1), *Laburnum alpinum* (2), *Erythrina variegata* (3), *Calopogonium mucunoides* (4), and *Millettia thonningii* (5). The angular isomer **29** of robustone is not known to occur in nature. In this paper, we report the synthesis of dihydropyranoisoflavones by the reaction of appropriate phenacyl chromans with ethoxalyl chloride/pyridine to give the carboethoxy isoflavones which were hydrolyzed and decarboxylated. It was observed that during decarboxylation, some angular isoflavone acids underwent decarboxylative rearrangement to linear dihydropyranoisoflavones. This is the first reported thermal rearrangement of dihydropyranoisoflavone carboxylic acids.

RESULTS AND DISCUSSION

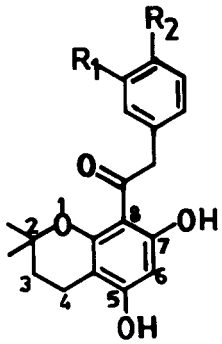
Phenacyl chroman **1** (6) was reacted with ethoxalyl chloride in pyridine (7) to give a mixture of the esters **6** and **7**, which were separated in a Si gel column and hydrolyzed to give the acids **8** and **9**. These, on decarboxylation, gave the isoflavones **25** and **12**. In order to confirm the identity of the products, phenacyl chroman **2** was reacted with ethoxalyl chloride in pyridine to give the carboethoxyisoflavone **10** which on hydrolysis to the acid **11** followed by decarboxylation gave the isoflavone **13**. This on demethylation gave a product which was identical with **12**. Hence, the ester and acid leading to **12** are assigned the angular structures **7** and **9**, while those corresponding to the isoflavone **25** have the linear structures **6** and **8**. Compound **25** on dehydrogenation with DDQ in C_6H_6 gave robustone [**28**], while **12** on dehydrogenation gave the angular isomer that has been named isorobustone [**29**].

In order to synthesize the corresponding angular isoflavones, phenacyl chromans **3–5** were treated with ethoxalyl chloride in pyridine to give the esters **14–16**, which were hydrolyzed to the acids **17–19**. However, the acids **17–19** on decarboxylation did not give the expected isoflavones **20–22**. The products obtained lacked absorption for a free OH in their ir spectra and showed a signal at δ 13.22 in their ^{1}H-nmr spectra for a chelated OH proton. The spectra of **14–16** and **17–19**, on the other hand, showed ir absorption for a free OH at 3350 and did not have the nmr signal at δ 13.22. Evidently decarboxylation is accompanied by rearrangement to give the linear isomer in which chelation of the OH-5 with the C-10 carbonyl renders the product thermodynamically

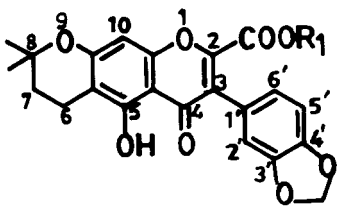
[1]Presented, in part, at the 10th International Congress of Heterocyclic Chemistry, Waterloo, Canada (1985).



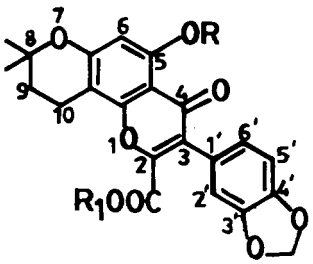
1 R=H
2 R=Me



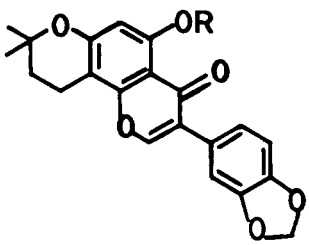
3 $R_1=R_2=H$
4 $R_1=H$, $R_2=OMe$
5 $R_1,R_2=-O-O-$



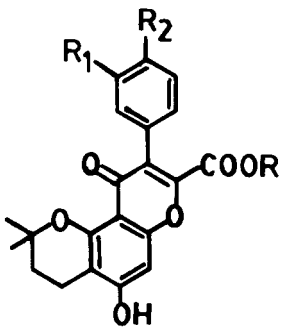
6 $R_1=Et$
8 $R_1=H$



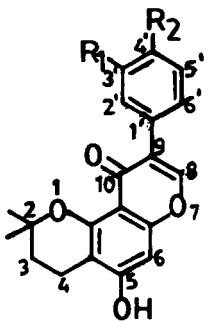
7 R=H, R_1=Et
9 R=R_1=H
10 R=Me, R_1=Et
11 R=Me, R_1=H



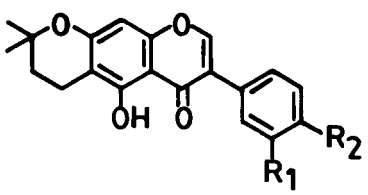
12 R=H
13 R=Me



14 R=Et, $R_1=R_2=H$
15 R=Et, R_1=H, R_2=OMe
16 R=Et, $R_1,R_2=-O-O-$
17 $R=R_1=R_2=H$
18 R=R_1=H, R_2=OMe
19 R=H; $R_1,R_2=-O-O-$

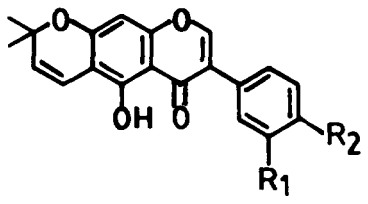


20 $R_1=R_2=H$
21 R_1=H, R_2=OMe
22 $R_1,R_2=-O-O-$

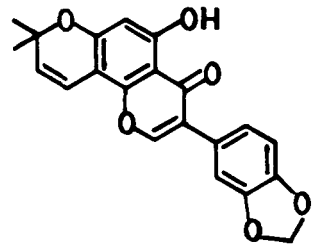


23 $R_1=R_2=H$
24 R_1=H, R_2=OMe
25 $R_1,R_2=-O-O-$

more stable. Further, the decarboxylated products were identical with **23–25**. The mechanism of the rearrangement may proceed as shown in Scheme 1. Dehydrogenation of **23–25** gave **26**, 4′-*O*-methylalpinum isoflavone [**27**] (8), and robustone [**28**].



26 $R_1=R_2=H$
27 $R_1=H$, $R_2=OMe$
28 $R_1,R_2=-O-O-$



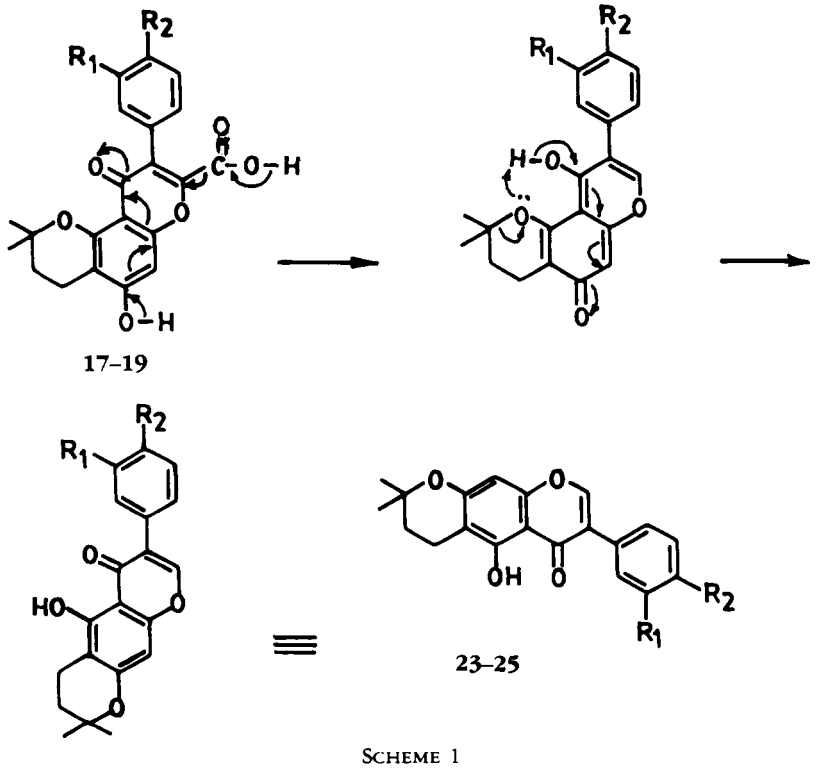
29

EXPERIMENTAL

GENERAL.—All melting points are uncorrected. Ir spectra (in Nujol) were recorded on a Perkin-Elmer 237 instrument. ^{1}H-nmr spectra (in $CDCl_3$) were recorded on a Varian XL-100 spectrometer (100 MHz) using TMS as internal standard. Chemical shifts are expressed in ppm. All compounds were characterized by their spectra and elemental analyses.

FORMATION OF CARBOETHOXY ISOFLAVONES **6** AND **7**.—Freshly distilled ethoxalyl chloride (2 ml, 17.60 mmol) was added slowly with stirring to a cooled solution of phenacyl chroman **1** (2 g, 5.60 mmol) in pyridine (20 ml), and the mixture was kept at 0° for 2 days, poured into H_2O, and extracted with $CHCl_3$. The extract was washed with diluted HCl and H_2O and dried (Na_2SO_4), and the solvent was evaporated. The residue showed two components on tlc and was chromatographed on Si gel. Elution with hexane-$CHCl_3$ (90:10 and 80:20) gave the fractions A and B.

CARBOETHOXY ISOFLAVONE **10**.—To phenacyl chroman **2** (1 g, 2.70 mmol) in pyridine (12 ml), ethoxalyl chloride (2 ml, 17.60 mmol) was added dropwise with stirring, and the mixture after keeping at 0° for 2 days was worked up as above.



17–19

23–25

SCHEME 1

CARBOETHOXYISOFLAVONES **14–16**.—Phenacyl chromans **3**, **4**, and **5** (1 g; 3.20, 2.92 or 2.80 mmol, respectively) were dissolved separately in pyridine (10 ml). Ethoxalyl chloride (2 ml, 17.60 mmol) was added, and the mixture was kept at 0° for 2 days. The solvent was removed and the product was purified by chromatography over Si gel to give compounds **14**, **15**, and **16**, respectively.

COMPOUND **6**.—Removal of solvent from fraction A gave a solid, which crystallized from the same solvent (720 mg, 29.5%): mp 183–184°; ir ν 3210, 1745, 1660, 1615 cm^{-1}; ^1H nmr δ 1.10 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.38 (6H, *gem*-methyls), 1.86 (2H, t, J = 7 Hz, H-7), 2.74 (2H, t, J = 7 Hz, H-6), 4.22 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 6.02 (2H, s, O-CH_2-O), 6.43 (1H, s, H-10), 6.70–6.92 (3H, m, aromatic H), 12.82 (1H, s, 5-OH). Found C 65.39, H 5.14; $C_{24}H_{22}O_8$ requires C 65.75, H 5.02%.

COMPOUND **7**.—Fraction B on removal of solvent gave a solid, which crystallized from the same solvent (750 mg, 30.5%): mp 176–177°; ir ν 3200, 1745, 1665 cm^{-1}; ^1H nmr δ 1.12 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.38 (6H, s, *gem*-methyls), 1.86 (2H, t, J = 7 Hz, H-9), 2.86 (3H, t, J = 7 Hz, H-10), 4.22 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 6.02 (2H, s, O-CH_2-O), 6.40 (1H, s, H-6), 6.72–6.92 (3H, m, aromatic H), 12.22 (1H, s, 5-OH). Found C 65.70, H 4.99; $C_{24}H_{22}O_8$ requires C 65.75, H 5.02%.

COMPOUND **10**.—The product crystallized from MeOH (750 mg, 61.5%): mp 117–118°; ir ν 1750, 1660 cm^{-1}; ^1H nmr δ 1.16 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.40 (6H, s, *gem*-methyls), 1.78 (2H, t, J = 7 Hz, H-9), 2.52 (2H, t, J = 7 Hz, H-10), 3.82 (3H, s, OMe), 4.20 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 5.98 (2H, s, OCH_2O), 6.38 (1H, s, H-6), 6.85–7.00 (3H, m, aromatic H). Found C 66.49, H 5.59; $C_{25}H_{24}O_8$ requires C 66.37, H 5.31%.

COMPOUND **14**.—Compound **14** crystallized from MeOH: mp 242–243°; ir ν 3450, 1720, 1640, 1610, 1570, 1450 cm^{-1}; ^1H nmr δ 0.94 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.42 (6H, s, *gem*-methyls), 1.84 (2H, t, J = 7 Hz, H-3), 2.68 (2H, t, J = 7 Hz, H-4), 4.14 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 6.50 (1H, s, H-6), 7.30–7.40 (5H, m, aromatic H), 8.32 (1H, s, 5-OH, D_2O exchangeable). Found C 69.96, H 5.47; $C_{23}H_{22}O_6$ requires C 70.05, H 5.58%.

COMPOUND **15**.—Compound **15** crystallized from MeOH; mp 260–262°; ir ν 3450, 1715, 1640, 1615 cm^{-1}; ^1H nmr δ 1.00 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.40 (6H, s, *gem*-methyls), 1.84 (2H, t, J = 7 Hz, H-3), 2.70 (2H, t, J = 7 Hz, H-4), 3.84 (3H, s, OMe), 4.14 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 6.52 (1H, s, H-6), 6.92 (2H, d, J = 8 Hz, H-3′, H-5′), 7.22 (2H, d, J = 8 Hz, H-2′, H-6′). Found C 67.62, H 5.84; $C_{24}H_{24}O_7$ requires C 67.92, H 5.66%.

COMPOUND **16**.—Compound **16** crystallized from MeOH: mp 254–255°; ir ν 3440, 1720, 1640, 1610 cm^{-1}; ^1H nmr δ 1.06 (3H, t, J = 7 Hz, $COOCH_2CH_3$), 1.42 (6H, s, *gem*-methyls), 1.84 (2H, t, J = 7 Hz, H-3), 2.68 (2H, t, J = 7 Hz, H-4), 4.20 (2H, q, J = 7 Hz, $COOCH_2CH_3$), 5.96 (2H, s, OCH_2O), 6.50 (1H, s, H-6), 6.60–6.70 (3H, m, aromatic H). Found C 65.56, H 5.14; $C_{24}H_{22}O_8$ requires C 65.75, H 5.02%.

HYDROLYSIS OF **6**, **7**, **10**, AND **14–16**: FORMATION OF ACIDS **8**, **9**, **11**, AND **17–19**.—The esters **6**, **7**, **10**, and **14–16** (500 mg each) were dissolved separately in Me_2CO (20 ml) and refluxed with aqueous Na_2CO_3 (5%, 15 ml) for 4 h. Removal of the solvent and acidification of the residual solution with HCl (1:1) afforded acids **8**, **9**, **11**, and **17–19**, respectively, which were filtered, washed, and crystallized from MeOH (90–92% yield).

ACID **8**.—Mp 226–228°. Found C 64.06, H 4.65; $C_{22}H_{18}O_8$ requires C 64.39, H 4.39%.

ACID **9**.—Mp 238–240°. Found C 64.21, H 4.78; $C_{22}H_{18}O_8$ requires C 64.39, H 4.39%.

ACID **11**.—Mp 220–221°. Found C 64.78, H 4.95; $C_{23}H_{20}O_8$ requires C 65.09, H 4.72%.

ACID **17**.—Mp 200–201°. Found C 68.49, H 5.12; $C_{21}H_{18}O_6$ requires C 68.85, H 4.92%.

ACID **18**.—Mp 215–217°. Found C 66.81, H 5.30; $C_{22}H_{20}O_7$ requires C 66.67, H 5.05%.

ACID **19**.—Mp 209–211°. Found C 64.42, H 4.56; $C_{22}H_{18}O_8$ requires C 64.39, H 4.39%.

DECARBOXYLATION OF ACIDS **7**, **9**, **11**, AND **17–19**: FORMATION OF DIHYDROPYRANOISOFLAVONES **25**, **12**, **13**, AND **23–25**.—Each of the acids **7**, **9**, **11**, and **17–19** (300 mg each) was heated separately in an oil bath to a temperature 10° above its melting point until the evolution of CO_2 ceased. The crude melt was treated with $NaHCO_3$ solution, filtered, and washed with H_2O to give the isoflavones **25**, **12**, **13**, and **23–25**, respectively (63–67% yield).

DIHYDROROBUSTONE [**25**].—Compound **25** crystallized from C_6H_6 (180 mg): mp 192–194°; ir ν 1660, 1610, 1575, 1520 cm^{-1}; ^1H nmr δ 1.38 (6H, s, *gem*-methyls), 1.84 (2H, t, J = 7 Hz, H-7), 2.74 (2H, t, J = 7 Hz, H-6), 6.02 (2H, s, OCH_2O), 6.35 (1H, s, H-10), 6.92–6.96 (3H, m, aromatic H),

7.84 (1H, s, H-2), 13.16 (1H, s, 5-OH). Found C 68.78, H 5.06; $C_{21}H_{18}O_6$ requires C 68.85, H 4.92%.

DIHYDROISOROBUSTONE [**12**].—Compound **12** crystallized from C_6H_6 (170 mg): mp 230–232°; ir ν 1660, 1615, 1580, 1520 cm^{-1}; ^1H nmr δ 1.38 (6H, s, *gem*-methyls), 1.86 (2H, t, J = 7 Hz, H-9), 2.80 (2H, t, J = 7 Hz, H-10), 6.04 (2H, s, OCH_2O), 6.30 (1H, s, H-6), 6.92–6.95 (3H, m, aromatic H), 7.90 (1H, s, H-2), 12.64 (1H, s, 5-OH). Found C 68.56, H 5.31; $C_{21}H_{18}O_6$ requires C 68.85, H 4.92%.

Compound **13** crystallized from C_6H_6 (160 mg): mp 180–181°; ir ν 1660, 1615, 1575, 1525 cm^{-1}; ^1H nmr δ 1.40 (6H, s, *gem*-methyls), 1.88 (2H, t, J = 7 Hz, H-9), 2.82 (2H, t, J = 7 Hz, H-10), 3.96 (3H, s, OMe), 6.00 (2H, s, OCH_2O), 6.34 (1H, s, H-6), 7.16 (3H, m, aromatic H), 7.82 (1H, s, H-2). Found C 69.61, H 5.35; $C_{22}H_{20}O_6$ requires C 69.47, H 5.26%.

DEMETHYLATION OF **13** TO **12**.—A mixture of **13** (80 mg, 0.21 mmol), anhydrous $AlCl_3$ (250 mg, 1.81 mmol), and MeCN (12 ml) was refluxed for 3 h, and the solvent was removed. The residue was heated with dilute HCl for 0.5 h on an H_2O bath, and the solid was filtered and washed with H_2O. It crystallized from C_6H_6 (40 mg, 52%), mp 230–232°. The product was identical with the isoflavone **12** (mmp, co-tlc, and superimposable ir spectra).

The product from **17** crystallized from EtOH, mp 194–195° [193–195°[2]] ir ν 1660, 1610, 1580 cm^{-1}, ^1H nmr δ 1.38 (6H, s, *gem*-methyls), 1.84 (2H, t, J = 7 Hz, H-7), 2.76 (2H, t, J = 7 Hz, H-6), 6.38 (1H, s, H-10), 7.38–7.54 (5H, m, aromatic H), 7.86 (1H, s, H-2), 13.22 (1H, s, 5-OH).

The product from **18** crystallized from EtOH, mp 176–178° [lit. (8) mp 177–179°], ir ν 1665, 1610, 1580 cm^{-1}; ^1H nmr δ 1.38 (6H, s, *gem*-methyls), 1.86 (2H, t, J = 7 Hz, H-7), 2.76 (2H, t, J = 7 Hz, H-6), 3.86 (3H, s, OMe), 6.38 (1H, s, H-10), 7.00 (2H, d, J = 8 Hz, H-3′, H-5′), 7.48 (2H, d, H-2′ and H-6′), 7.84 (1H, s, H-2), 13.22 (1H, s, 5-OH). It was identical with an authentic sample of **24** reported earlier (mp, mmp, ir, and ^1H-nmr spectra) (8).

The product from **19** crystallized from EtOH: mp 194–196°; ir ν 1665, 1610, 1575 cm^{-1}, and was identical with the linear product **25** from phenacyl chroman **1**.

DEHYDROGENATION OF **23–25** AND **12**: FORMATION OF PYRANOISOFLAVONES **26–29**.—Compounds **23–25** and **12** (80 mg each) were each added separately to C_6H_6 (25 ml); DDQ (170 mg) was added and the mixture was refluxed for 20 h and cooled and the hydroquinone filtered off. Removal of solvent gave the pyranoisoflavones (56–58% yield).

PYRANOISOFLAVONE [**26**].—Compound **26** was obtained as a thick viscous liquid which could not be crystallized: ir ν 1620 cm^{-1}; ^1H nmr δ 1.48 (6H, s, *gem*-methyls), 5.65 (1H, d, J = 10 Hz, H-7), 6.36 (1H, s, H-10), 6.75 (1H, d, J = 10 Hz, H-6), 7.50 (5H, m, aromatic H), 7.88 (1H, s, H-2), 13.14 (1H, s, 5-OH). Found C 74.96, H 5.17; calcd for $C_{20}H_{16}O_4$, C 75.00, H 5.00%.

4′-*O*-METHYLALPINUM ISOFLAVONE [**27**].—Compound **27** crystallized from Me_2CO/hexane (30 mg), mp 135–137° [lit. (8) 135–137°], ir ν 1655, 1615 cm^{-1}.

ROBUSTONE [**28**].—Compound **28** crystallized from MeOH (45 mg): mp 172–174° [172–173[2]], ir ν 1660, 1620 cm^{-1}; ^1H nmr δ 1.46 (6H, s, *gem*-methyls), 5.62 (1H, d, J = 10 Hz, H-7), 5.96 (2H, s, OCH_2O), 6.26 (1H, s, H-10), 6.70 (1H, d, J = 10 Hz, H-6), 6.90–7.08 (3H, m, aromatic H), 7.90 (1H, s, H-2), 13.14 (1H, s, 5-OH).

ISOROBUSTONE [**29**].—Compound **29** crystallized from MeOH: mp 142–143°; ir ν 1660, 1615 cm^{-1}; ^1H nmr δ 1.48 (6H, s, *gem*-methyls), 5.60 (1H, d, J = 10 Hz, H-9), 6.02 (2H, s, -OCH_2O), 6.31 (1H, s, H-6), 6.70 (1H, d, J = 10 Hz, H-10), 6.92–7.05 (3H, m, aromatic H), 7.91 (1H, s, H-2), 12.90 (1H, s, 5-OH). Found C 69.06, H 4.62; $C_{21}H_{16}O_6$ requires C 69.23, H 4.40%.

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