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SYNTHESIS OF (±)-NEORAUTANE

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ABSTRACT.—A synthesis of the racemate of the naturally occurring pterocarpan (−)-neorautane [7] has been carried out. The key intermediate required for the synthesis, the chromene **6**, was prepared from benzodihydropyran [1] through a series of steps and was reacted with 2-chloromercurio-4,5-methylene dioxy phenol in the presence of lithium chloropalladite to yield (±)-neorautane [7]. Treatment of **7** with DDQ gave the coumestan **8**, while bromination with *N*-bromosuccinimide followed by treatment with pyridine afforded the pterocarpene **9**.

Several pterocarpans have been isolated from natural sources and reported to possess antifungal (1) and antitumor (2) activity. These include simple pterocarpans and those with either a 2,2-dimethyl-2*H*-pyrano or a 2,2-dimethyl-3,4-dihydro-2*H*-pyrano moiety as part of their structure. (−)-Neorautane [7] isolated from the root bark of *Neorautanania edulis* (3) belongs to the last group.

In continuation of our work on the synthesis of natural heterocycles from compounds with a built-in 2,2-dimethyl-3,4-dihydro-2*H*-pyran moiety, (±)-neorautane has now been synthesized from the chromene **6**, which has the requisite framework; hence, it is only required to build up the pterocarpan structure on it. Such an approach forms the basis of the work reported here.

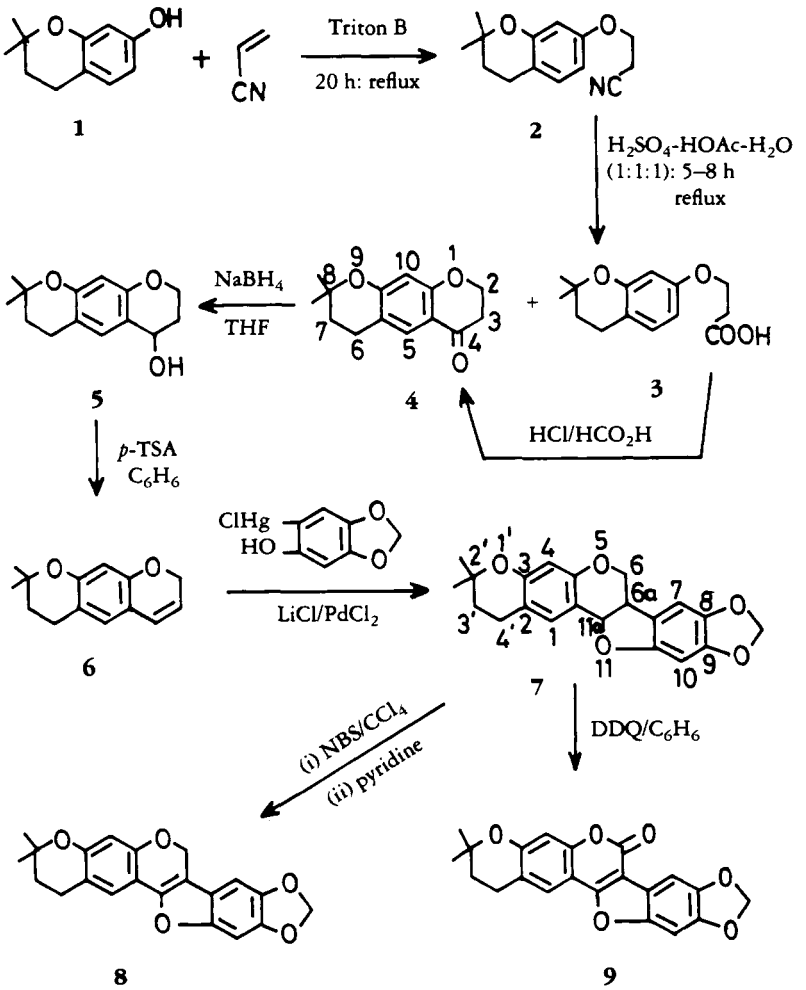
The chromene **6** required for the synthesis of **7** was prepared as shown in Scheme 1. Benzodihydropyran [**1**] on reaction with acrylonitrile in the presence of Triton B or NaOMe gave the nitrile **2** which was hydrolysed to yield a mixture of two products, A and B; these were separated on a Si gel column. From the ir and ^{1}H-nmr spectral data, compound A was identified as the acid **3** and compound B as the chromanone **4**. The acid formed on hydrolysis has partially cyclized to the chromanone. The uncyclized acid was cyclized to the chromanone using polyphosphoric acid (PPA) and also HCl/HCO_2H. The chromanone **4** could also be obtained by the Hoesch reaction of nitrile **2**. Reduction of **4** with $NaBH_4$ in THF gave the chromanol **5** which was dehydrated to the chromene **6** with *p*-TSA. Condensation of **6** with 2-chloromercurio-4,5-methylenedioxyphenol (4,5) in presence of lithium chloropalladite in Me_2CO gave (±)-neorautane [7].

Treatment of **7** with DDQ in C_6H_6 gave the coumestan derivative **8**, while on bromination with *N*-bromosuccinimide (NBS) followed by dehydrobromination with pyridine, the pterocarpene **9** was obtained. These results are interesting in that in both the cases, the dihydropyran moiety did not get dehydrogenated. Evidently, the formation of coumestan appears to be more facile due to extended conjugation in the α,β-unsaturated system. The NBS/pyridine product did not show any olefinic protons, and further the 6a, 11a protons were absent in the nmr spectrum confirming the formation of the pterocarpene. All the compounds were characterized by analytical and spectral data.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points are uncorrected. The ir spectra in Nujol were recorded on a Perkin-Elmer model 237 spectrometer. The ^{1}H nmr spectra in $CDCl_3$ were recorded on a Varian XL-100 spectrometer (100 MHz) with TMS as internal standard.

PREPARATION OF 7-(2′-CYANOETHOXY)-2,2-DIMETHYL-3,4-DIHYDRO-2*H*-1-BENZOPYRAN [**2**].—To a mixture of benzodihydropyran **1** (5 g) and acrylonitrile (30 ml), Triton B (2 ml) was added slowly and the mixture refluxed in an oil bath for 20 h, cooled, and extracted with Et_2O. The organic layer



SCHEME 1

was washed with NaOH (5%), dilute HCl, and H_2O and dried (Na_2SO_4). Removal of solvent gave a white solid which crystallized from hexane/C_6H_6 as needles (4.8 g, 74%), mp 89–91°; ir ν 2220, 1620, 1580, 1380, 1370 cm^{-1}; ^1H nmr δ 1.36 (2 × 3H, s, *gem*-methyls), 1.80 (2H, t, $J = 7$ Hz, H-3), 2.64–2.86 (2 × 2H, m, CH_2CN, H-4), 4.08 (2H, t, $-OCH_2$), 6.38 (1H, s, H-8), 6.50 (1H, d, $J = 8$ Hz, H-5), 7.00 (1H, d, $J = 8$ Hz, H-6). Found C 73.00, H 7.40; $C_{14}H_{17}NO_2$ requires C 72.70, H 7.30.

In another method a mixture of benzodihydropyran (5 g), acrylonitrile (30 ml), and NaOMe (1 g) was refluxed for 7 h and excess acrylonitrile was removed. The residual mass was extracted with Et_2O, washed with H_2O, and dried (Na_2SO_4), and the solvent was removed to give a solid which crystallized from hexane/C_6H_6 as needles (4.5 g, 69%), mp 89–91°.

HYDROLYSIS OF NITRILE **2**.—To the nitrile **2** (4 gm), H_2SO_4-HOAc-H_2O (1:1:1) (5 ml) was added, and the mixture was heated on an H_2O bath for 5 h, poured into H_2O, and extracted with Et_2O; the Et_2O layer was washed with H_2O and dried (Na_2SO_4). Removal of solvent gave a dark residue which showed two spots on tlc. The mixture was chromatographed over Si gel and eluted with hexane-EtOAc (90:10 and 80:20) to give fractions A and B, respectively.

8,8-DIMETHYL-6,7-DIHYDRO[1,2-*b*: 5,4-*b'*]-2*H*,8*H*-BENZOPYRAN-4-ONE [**4**].—Removal of solvent from fraction A gave a solid which crystallized from hexane as white plates (600 mg, 15%), mp 81–83°; ir ν 1690, 1625, 1580, 1380, 1375 cm^{-1}; ^1H nmr δ 1.36 (2 × 3H, s, *gem*-methyls), 1.80 (2H, t, $J = 7$ Hz, H-7), 2.64–2.82 (2 × 2H, m, H-3 and H-6), 4.50 (2H, t, $J = 7$ Hz, H-2), 6.34 (1H, s, H-10), 7.68 (1H, s, H-5). Found C 72.56, H 6.99; $C_{14}H_{16}O_3$ requires C 72.41, H 6.90%.

7-*O*-(2-CARBOXYETHYL)-2,2-DIMETHYL-3,4-DIHYDRO-2*H*-1-BENZOPYRAN [**3**].—Removal of solvent from fraction B gave a solid which crystallized from C_6H_6/hexane as white needles (900 mg, 21%), mp 122–123°, ir ν 1710, 1620, 1580, 1380, 1375 cm^{-1}; ^1H nmr δ 1.38 (6H, s), 1.80 (2H, t), 2.64–2.90 (4H, m), 4.26 (2H, t), 6.40 (1H, s), 6.50 (1H, d, J = 8 Hz), 6.98 (1H, d, J = 8 Hz), 11.40 (1H, s). Found C 66.80, H 7.30; $C_{14}H_{18}O_4$ requires C 67.30, H 7.20%.

CYCLIZATION OF **3** TO **4**.—The acid **3** (400 mg) was added slowly to mixture of P_2O_5 (4 g) and H_3PO_4 (2 ml) preheated at 100°, and the heating was continued for 2 h with occasional shaking. The mixture after cooling was decomposed with H_2O and extracted with Et_2O; the extract was washed with $NaHCO_3$ solution and H_2O and dried (Na_2SO_4). The solvent was removed to give a dark residue which was purified on a Si gel column by eluting with hexane-EtOAc (90:10). The product crystallized from C_6H_6/hexane to give **4**, mp 81–83°. The acid could also be cyclized using HCl/HCO_2H.

HOESCH REACTION OF NITRILE **2**.—To the nitrile **2** (4 g) dissolved in dry Et_2O (125 ml), fused $ZnCl_2$ (5 g) was added, and dry HCl gas was passed at 0° until saturation was reached. The mixture was left in the refrigerator for 48 h. The Et_2O was decanted and the ketimine hydrochloride was hydrolyzed with H_2O on a steam bath, cooled, extracted with Et_2O, and dried (Na_2SO_4). Removal of the solvent gave a solid which crystallized from hexane to give **4** as white plates (2 g, 50%), mp 81–83°.

REDUCTION OF **4** TO CHROMANOL **5**.—A mixture of **4** (800 mg), $NaBH_4$ (1.6 g), and THF (40 ml) was refluxed in an oil bath for 20 h after which the THF was removed under reduced pressure. Workup of the residue gave a solid which crystallized from hexane as white needles (700 mg, 86%), mp 85–86°; ir ν 3300, 1630, 1580, 1380, 1375 cm^{-1}; ^1H nmr δ 1.36 (6H, s), 1.80 (2H, t, J = 7 Hz, H-7), 2.04 (2H, m, H-3), 2.70 (2H, t, J = 7 Hz, H-6), 4.24 (2H, t, J = 7 Hz, H-2), 4.68 (1H, t, J = 5.5 Hz, H-4), 6.30 (1H, s, H-10), 7.02 (1H, s, H-5). Found C 71.82, H 7.77; $C_{14}H_{18}O_3$ requires C 71.79, H 7.69%.

DEHYDRATION OF **5** TO CHROMENE **6**.—The chromanol **5** (600 mg) was dissolved in C_6H_6 (15 ml) to which *p*-toluene sulfonic acid (5 mg) was added, and the mixture was heated at 70° for 30 min, cooled, washed with $NaHCO_3$ solution and H_2O, and dried (Na_2SO_4). The dark yellow residue left after removal of solvent was chromatographed on a Si gel column and eluted with hexane-EtOAc (95:5). The solvent was removed to give tlc pure **6** as a pale yellow liquid (420 mg, 76%); ^1H nmr δ 1.36 (2 × 3H, s, *gem*-methyls), 1.80 (2H, t, J = 7 Hz, H-7), 2.72 (2H, t, J = 7 Hz, H-6), 4.60 (2H, m, H-2), 5.52 (1H, m, H-3), 6.26 (1H, m, H-4), 6.42 (1H, s, H-10), 7.70 (1H, s, H-5). Found C 77.59, H 6.96; $C_{14}H_{16}O_2$ requires C 77.75, H 7.40%.

SYNTHESIS OF (±)-NEORAUTANE [**7**].—Palladium dichloride (240 mg) and lithium chloride (250 mg) were mixed with dry Me_2CO (15 ml) and to this was added the chromene **6** (300 mg) in dry Me_2CO (5 ml). After stirring the mixture for 30 min, 2-chloromercurio-4,5-methylenedioxyphenol (500 mg) in dry Me_2CO (12 ml) was added and the stirring was continued for 3 h at room temperature. The mixture was shaken with saturated brine and extracted with C_6H_6 and dried (Na_2SO_4). Removal of solvent and chromatography of the dark residue over Si gel [eluent: hexane-EtOAc (95:5)] gave **7** which crystallized as white flakes from the same solvent mixture (290 mg, 59%), mp 170–171°, ir ν 1620, 1580, 1380, 1370 cm^{-1}; ^1H nmr δ 1.36 (2 × 3H, s, *gem*-methyls), 1.80 (2H, t, J = 7 Hz, H-3′), 2.78 (2H, t, J = 7 Hz, H-4′), 3.56 (1H, m, H-6a), 3.60 (1H, m, H-6ax), 4.26 (1H, m, H-6eq), 5.70 (1H, d, J = 6 Hz, H-11a), 5.94 (2H, s, OCH_2O), 6.40 (1H, s, H-4), 6.70 (1H, s, H-10), 6.76 (1H, s, H-7), 7.24 (1H, s, H-1). Found C 71.70, H 5.69; calcd for $C_{21}H_{20}O_5$, C 71.59, H 5.68%.

FORMATION OF COUMESTAN **8**.—Compound **7** (80 mg) was refluxed with DDQ (200 mg) in C_6H_6 (25 ml) for 12 h. The precipitated hydroquinone was filtered, and the solvent was removed from the filtrate. The residue was purified by passing through a Si gel column and eluting with C_6H_6. The product crystallized from hexane/C_6H_6 as white needles (40 mg, 48%), mp 258–260°; ir ν 1740, 1630, 1580, 1380, 1375 cm^{-1}; ^1H nmr δ 1.40 (2 × 3H, s, *gem*-methyls), 1.88 (2H, t, J = 7 Hz, H-3′), 2.90 (2H, t, J = 7 Hz, H-4′), 6.06 (2H, s, OCH_2O), 6.88 (1H, s, H-4), 7.10 (1H, s, H-10), 7.26 (1H, s, H-7), 7.64 (1H, s, H-1). Found C 69.48, H 4.62; $C_{21}H_{16}O_6$ requires C 69.23, H 4.40%.

FORMATION OF PTEROCARPENE **9**.—A mixture of **7** (100 mg), NBS (60 mg), and dibenzoyl peroxide (5 mg) in CCl_4 (12 ml) was refluxed for 3 h, cooled and worked up. The residue obtained was heated to reflux with pyridine (3 ml) for 2 h. Removal of solvent and purification of the residue in a Si gel column gave **9** (55 mg, 55%). It crystallized from C_6H_6 as pale yellow needles, mp 213–215°; ir ν 1630, 1580, 1380, 1375 cm^{-1}; ^1H nmr δ 1.40 (2 × 3H, s, *gem*-methyls), 1.98 (2H, t, J = 7 Hz, H-3′), 2.90 (2H, t, J = 7 Hz, H-4′), 6.00 (2H, s, H-6), 6.08 (2H, s, OCH_2O), 6.80 (1H, s, H-4), 7.10 (1H, s, H-10), 7.20 (1H, s, H-7), 7.62 (1H, s, H-1). Found C 71.82, H 4.92; $C_{21}H_{18}O_5$ requires C 72.00, H 5.14%.

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