

SYNTHESIS OF TETRAHYDRO-
-6H-BENZO [4,5] PYRANO [2,3-c] PYRIDIN-6-ONE
A NOVEL RING SYSTEM[†]

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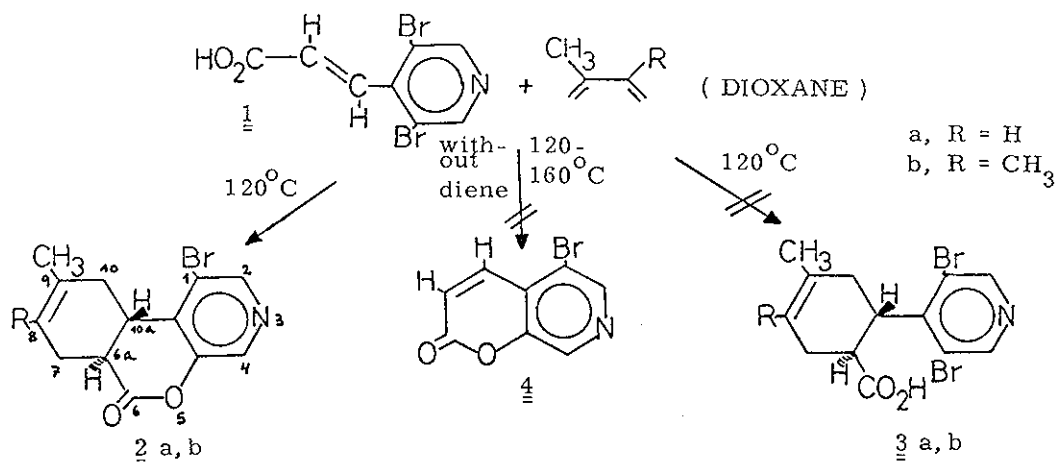
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1-Bromo-(8),9-(di) methyl -6a,10a-trans-6a,7,10,10a tetrahydro 6H-benzo [4,5] pyrano [2,3-c] pyridin -6-one is synthesized by means of a Diels-Alder reaction, starting from trans-4-(3,5 dibromo) pyridil- acrylic acid, in a one-step procedure.

In order to obtain pyridyl-analogues of Δ^8 -tetrahydrocannabinols (Δ^8 -THC) we prepared a 6H-benzo [4,5] pyrano [2,3-c] pyridine structure representing to our knowledge a new ring-system.

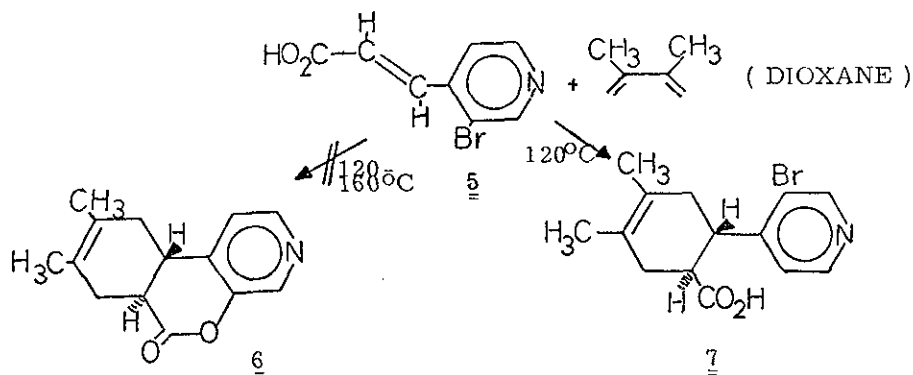
Reacting trans-4-(3,5 dibromo)-pyridyl acrylic acid 1 (obtained by means of a Knoevenagel-condensation of the corresponding pyridine aldehyde and malonic acid¹⁾ with isoprene or 2,3-dimethyl-butadiene in dioxane at 120°C, 14 hours, we obtained the lactonic structure 2 a,b (30% yield, mp.a: 151, b: 148°C) and not the "open" adduct 3 a,b, as expected from analogous reactions^{2,3)}.

[†]Dedicated to Professor Dr. Shigehiko Sugawara on the occasion of his eightieth birthday.



We presume that the Diels-Alder addition occurred with 1 as dienophile leading to the cyclohexenyl acid 3 a,b that rapidly cyclized to 2 a,b. Thus the configuration of the C-6a and 10a-protons is trans because of the stereospecificity of the cis-addition^{4,5}). This is an important result for the further synthesis of potentially active THC-structures⁶). The fact that we could not obtain the other possible dienophile, the 7-azacumarine 4, treating the dibromo-pyridyl acrylic acid 1 under similar conditions (in dioxane at 120 - 160°C) but without the diene, enhances our statement.

Similarly, we tried to synthesize the lactone 6 starting from the corresponding 4-(3-bromo)-pyridyl acrylic acid¹⁾ under the same or even more drastic reaction conditions (dioxane, 120 - 160°C). Here, we obtained exclusively the pyridylcyclohexenyl acid 7 (mp: 194°C, yield: 65%).



Probably, the mono-brominated derivate 5 is less activated than its analogous dibromo-pyridyl product 1 toward nucleophilic displacement reactions. The use of stronger polar, aprotic solvents to favour the reaction failed because under such conditions the diene tends to polymerize, subtracting them from the reaction mixture.

The structure of 2 a,b was proved using the following spectroscopic data: IR (KBr): ν C=O 1760 cm^{-1} , compatible with six-membered lactones, and absence of ν OH, which excludes an carboxilic acid structure. MS: $M^+ : a = 308$, $b = 294$, with M^+ peak-pattern characteristic for one bromine atom. Elementary analysis agreed also with the proposed formulas. $^1\text{H-NMR}$ (CDCl_3 , TMS): The aromatic protons appeared as two separated singlets at $\delta = 8.3$ and 8.5 ppm . The signals at $\delta = 3.5\text{ ppm}$ (m, $J = 7\text{ cps}$), 1H and 3.0 ppm (t, $J = 7\text{ cps}$), 1H were assigned to the protons at C - 6a and 10a respectively. C-7 and 10-protons appeared at $\delta = 2.7 - 1.6\text{ ppm}$ and the methyl groups (as broad singlets) at 1.6 and 1.7 ppm (b) and 1.7 ppm (a).

The "open" adduct 7 presents the following data: IR (KBr): $\nu_{\text{C=O}}$ 1700 cm^{-1} , ν_{OH} 3200 - 2700 cm^{-1} (-COOH); MS: $M^+ = 310$, 1 Br. $^1\text{H-NMR}$ (CDCl_3 , TMS): $\delta = 9.5$ ppm, s, 1H, changeable with D_2O (-COOH). $\delta = 8.4$, s, 1H; $\delta = 8.2$ and 7.1, two doublets, $J = 7$ cps, 1H each, (aromatic protons). The cyclohexene-part presents unsharp signals because of its ability for rapid conformational changes; one of the methine-protons vicinal to the carboxylic or to the aromatic group appeared at $\delta = 3.5$ ppm (m, 1H), whereas the other is shifted toward higher fields (2.4 - 2.0 ppm). The methyl groups present a broadened singlet at 1.7 ppm, 6H.

The obtained benzopyranopyridin-6-one structure 2 a,b represents a novel ring-system that can be transformed into 3-azacannabinoids¹⁾.

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