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CHEMICAL MODIFICATION OF PLANT ALKALOIDS. 4. REACTION OF COTARNINE WITH BIFUNCTIONAL NH- AND CH-ACIDS

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1-Substituted 1,2,3,4-tetrahydroisoquinoline systems were prepared by reaction of cotarnine with the NH- and CH-acids methyl- and acyl derivatives of pyrazole and 1,3-dicarbonyl reagents. Depending on the structure and reaction conditions, bifunctional pyrazole nucleophiles can give substitution products at the N atom, methyl, or acyl group; 1,3-diketones, at the terminal methyl. Rearrangements occurring during the reaction of cotarnine with bifunctional substrates were studied.

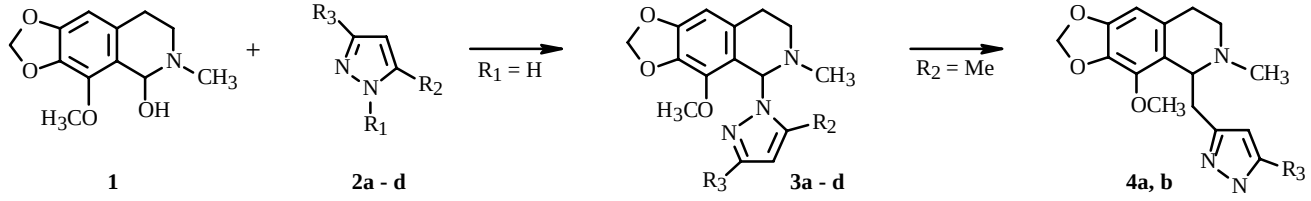
Key words: cotarnine, pyrazoles, 1,3-dicarbonyls, rearrangement.

6-Methyl-5-hydroxy-4-methoxy-5,6,7,8-tetrahydro-2*H*-1,3-methylenedioxy-[4,5-*g*]isoquinoline, or cotarnine (**1**), is a natural tautomeric pseudobase that is known to react with NH- and CH-acids to form the corresponding "anhydrocotarnyl derivatives" [1], which are of interest as structural analogs of isoquinoline plant alkaloids. The preparation of cotarnine adducts with NH-acids such as aniline, phenylhydrazine, urea [2-4], and indoles [5] has been reported. Among the CH-acids, HCN [6], ketones (acetone and acetphenone), nitroalkanes (CH_3NO_2 et al.), nitrotoluenes, phenylacetonitrile [7], cyclic β-dicarbonyls [8, 9], and compounds from certain other classes have been examined.

The mechanism of the reaction is an aminoalkylation. The reaction products are cyclic Mannich bases [10]. The limited set of examined nucleophilic substrates must be noted because it leaves the synthetic possibilities of cotarnine and related pseudobases mostly unexplored. Reactions of cotarnine with bifunctional nucleophilic reagents are very little studied.

In consideration of this and in continuation of studies of the synthesis of new analogs of isoquinoline alkaloids, we examined the reaction of **1** with a series of polyfunctional substrates including pyrazole, its methyl and acyl derivatives, and certain β-dicarbonyls.

The reaction of **1** with unsubstituted pyrazole (**2a**) in CH_3OH at 30°C proceeded rapidly to form the aminoalkylation product of pyrazole at the N atom **3a**. Considering the lability of cotarnine N-adducts, it can be assumed that electrophilic attack under more forcing conditions would lead to substitution at the C atom of the heteroaromatic ring, as occurred for indole [5]. However, **3a** turned out to be stable and isomerization was not observed on boiling in aqueous alcohol for 1 d.



1 **2a - d** **3a - d** **4a, b**

a: $R_1 = R_2 = R_3 = H$
b: $R_1 = H$, $R_2 = R_3 = Me$
c: $R_1 = R_2 = R_3 = Me$
d: $R_1 = R_3 = H$, $R_2 = Me$

a: $R_2 = R_3 = H$
b: $R_2 = R_3 = Me$
c: $R_2 = H$, $R_3 = Me$
d: $R_2 = Me$, $R_3 = H$

a: $R_3 = Me$
b: $R_3 = H$

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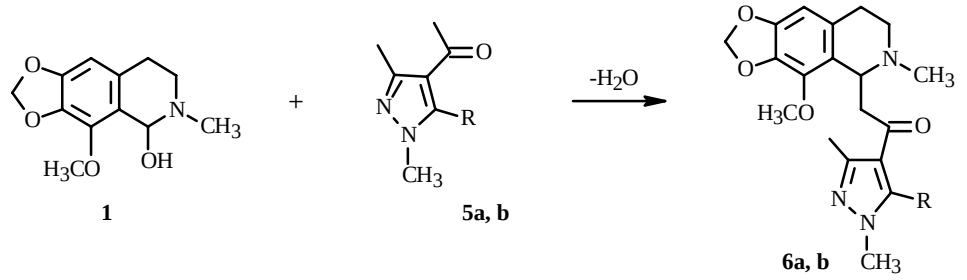
Reaction of **1** with 3,5-dimethylpyrazole (**2b**) in aqueous methanol at 30°C produced the N-substituted pyrazole derivative **3b**, which was stable in the crystalline state and in solutions in slightly polar solvents ($CHCl_3$, ether). However, it isomerized in aqueous alcohol to the thermodynamically more stable **4a**. At 70°C, this conversion was complete after 1 h. It is interesting that electrophilic attack of cotarnine at the analogous methyl of pyrazole derivatives that have no active NH proton was impossible due to its low reactivity, for example, 1,3,5-trimethylpyrazole (**2c**), which does not undergo the corresponding reaction even under more forcing conditions. Taking this into consideration, it can be assumed that the pyrazolyl methyl was activated during rearrangement of the N-adduct **3b** into the C-isomer **4a** by an intramolecular migration of the tetrahydroisoquinoline substituent.

3-Methylpyrazole (**2d**) reacted readily with **1** in CH_3OH to form a mixture of two isomeric N-adducts (**3c** and **3d**) in a 5:1 ratio according to ^1H NMR spectra. In contrast with the 3,5-dimethylpyrazole N-adduct **3b**, N-adducts **3c** and **3d** were much less prone to the analogous rearrangement. Thus, heating at 70°C for 1 h produced no evidence of formation of the corresponding derivative **4b**. Furthermore, prolonged heating (24 h) of a reaction mixture containing **3c** and **3b** led mainly to decomposition.

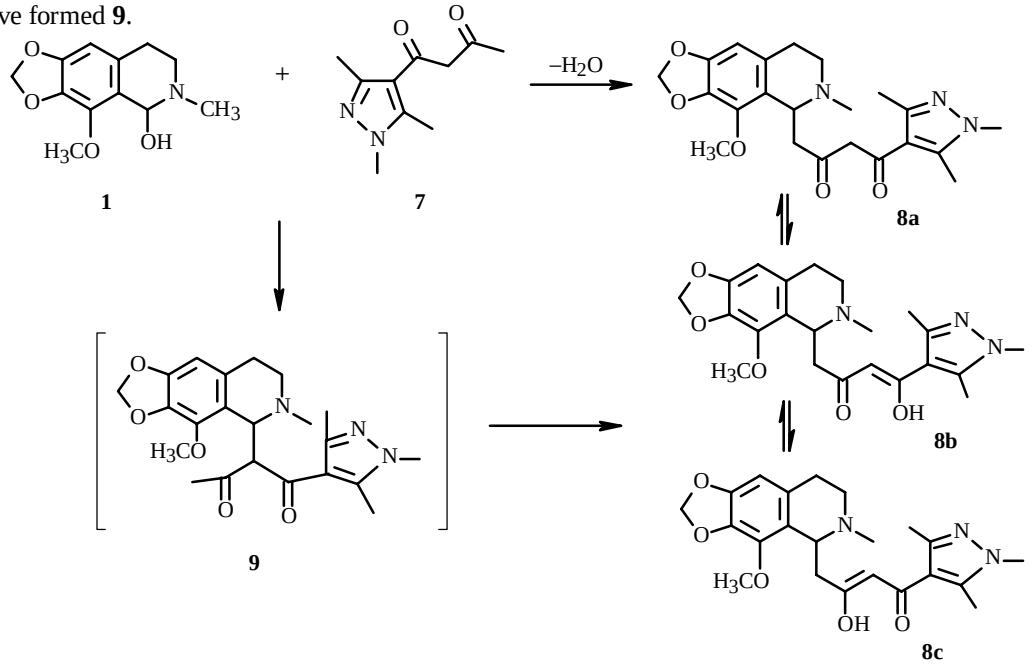
The 4-acetyl derivatives of 1,3-dimethyl- (**5a**) and 1,3,5-trimethylpyrazole (**5b**) reacted with **1** in CH_3OH to form substitution products at the acetyl **6a** and **6b**. These adducts were stable, did not decompose upon prolonged boiling in aqueous alcohol, and produced no evidence of transformation into the theoretically possible pyrazolylmethyl-substituted isomers.



1 **5a, b** **6a, b**

a: R = H; **b:** R = Me

We isolated **8a** from the reaction of **1** with 4-acetoacetyl-1,3,5-trimethylpyrazole (**7**), the product of substitution at the terminal methyl of the 1,3-diketone, and identified it using PMR spectra. This result was considered unexpected because 1,3-diketones reacting as nucleophiles usually give products of substitution at the acidic CH of the α-methylene. In this instance, this should have formed **9**.

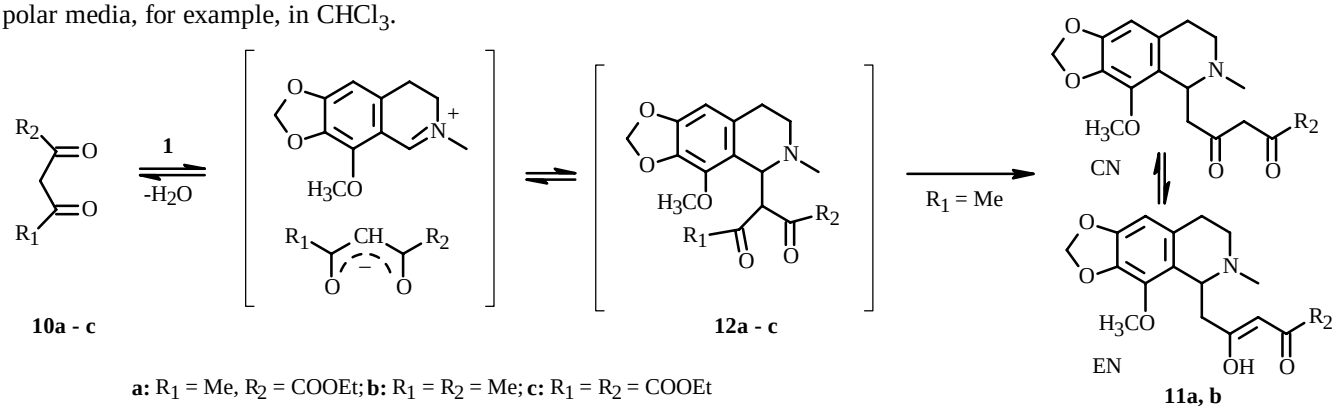


1 **7** **8a** **8b** **9** **8c**

Compound **8a** existed as a tautomer. The PMR spectra indicated that the enol form predominated in $CHCl_3$ solution (probably a mixture of spectrally indistinguishable forms **8b** and **8c** totaling 68-69%). The fraction of the corresponding

dicarbonyl form **8a** was 31-32%. For a quantitative estimate of the content of **8b** and **8c**, the most informative signals in the PMR spectrum were the singlet at 5.76 ppm (vinyl CH) and the broad singlet at 16.44 ppm (chelated OH proton). An AB quartet of methylene ($COCH_2CO$) at 3.94 ppm was characteristic of the dicarbonyl form **8a**. Signals in the spectra were identified based on standard methods of 2D ^1H—^1H NMR and by comparison with known related structures.

A study of the reaction of **1** with other 1,3-dicarbonyls showed that formation of the substitution product at the terminal methyl of the ketone is a common feature of these reactions. The ethyl ester of acetoacetic acid (**10a**) reacted with **1** in CH_3OH to form **11a**. Acetylacetone (**10b**) formed analogously **11b**. The reaction proceeded efficiently in not only polar but also slightly polar media, for example, in $CHCl_3$.



10a - c **12a - c** **11a, b**

a: R_1 = Me, R_2 = COOEt; **b:** R_1 = R_2 = Me; **c:** R_1 = R_2 = COOEt

a: R_2 = COOEt; **b:** R_2 = Me

We used PMR spectroscopy to establish the structures of tautomeric **11a** and **11b**.

The acetoacetic-acid derivative **11a** existed in $CDCl_3$ solution at 20°C and 0.2 M primarily as the dicarbonyl form (CN, 98%). The fraction of the corresponding enol form (EN) that was calculated from the strength of the vinyl-proton signal in the PMR spectra was ~2%. This was rather low compared with similar systems. For example, unsubstituted acetoacetic ester (**10a**) in slightly polar solvents is enolized by ~30% (29.4% in ether and 36.2% in CCl_4) according to the literature [7]. On the other hand, acetylacetone derivative **11b** existed in solutions primarily as the EN form. In $CHCl_3$, the content of the enol tautomer was 76%; in DMSO, 64%. In this sense, **11b** differed little from unsubstituted diketone **10b**, which, according to the literature, enolized by 81% in $CHCl_3$; 60% in DMSO [7].

Reacting **1** with diethylmalonate (**10c**) in $CHCl_3$ led to the isolation of **12c**, which is substituted at the α-C of the 1,3-dicarbonyl. The α-adduct **12c** was a relatively unstable compound that was reversibly hydrolyzed in the presence of water into the starting materials **1** and **10c**.

The lability of **12c** and its high formation rate indicate that the reaction of **1** with 1,3-dicarbonyls such as **7**, **10a**, and **10b** involves an intermediate of the corresponding α-adducts such as **12a**, which then rearrange into the more stable derivatives **8a**, **11a**, and **11b**, which are substituted at the terminal methyl.

The following arguments can be given in favor of this two-step reaction mechanism. It is known that the α-methylene in **10a** and **10b** has distinct CH-acidity (pKa for aqueous solutions of 10.75 and 9.00, respectively [7]). Therefore, addition of a base such as **1** (pK_B 12.6 [1]) should deprotonate these acids to form the corresponding monoanions in pairs with the cation (**1a**). Recombination of this ion pair can lead to the corresponding α-adduct of type **12a** whereas attack at the unactivated methylketone under similar conditions seems improbable. After the α-adduct forms, it can isomerize into the more stable system through migration of a 1,2,3,4-tetrahydroisoquinoline fragment onto the terminal methyl. A rearrangment of this type, which requires preliminary deprotonation of the $COCH_3$, is apparently more easily accomplished through an intramolecular mechanism involving a six-membed cyclic transition state.

Thus, the results indicate that substrates **2b**, **7**, **10a**, and **10b**, which have several centers for electrophilic attack, react during aminoalkylation of **1** with substitution of the more active protons. However, the adducts formed by this are less stable and can rearrange into stabler isomers. The studied features have fundamental significance for carrying out regiospecific synthesis of substituted 1,2,3,4-tetrahydroisoquinolines from **1** and polyfunctional nucleophilic reagents.

EXPERIMENTAL

PMR spectra were recorded in $CDCl_3$ on a Bruker AM-500 (500 MHz) spectrometer. The purity of the products was monitored using PMR spectra, elemental analyses, and TLC (on Silufol UV-254 plates using $CHCl_3$:EtOAc, 1:1; propan-2-ol:water, 4:1; and DMF:NH_4OH (25%), 10:1).

Compounds **2a-d** and **10a-c** were used as received. Compounds **5a** [8] and **5b** and **7** [9] were prepared as before. Their physicochemical properties agreed with those in the literature.

4-Methoxy-6-methyl-5,6,7,8-tetrahydro-2*H*-1,3-methylenedioxy-[4,5-*g*]isoquinolin-5-ol (cotarnine) 1 was isolated from an aqueous solution of cotarnine chloride (pharm.) using NaOH solution (10%) by the literature method [5], mp 130-132°C.

5-(1*H*-Pyrazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (3a). A solution of **1** (1.18 g, 5 mmol) in CH_3OH (10 mL) at 30°C was treated with a solution of pyrazole (**2a**, 0.34 g, 5 mmol) in CH_3OH (5 mL) and H_2O (2 mL). The solution was held for 1 h at room temperature. The resulting crystals were separated, washed with CH_3OH, and dried in air to afford **3a** (1.29 g, 89%) as colorless crystals, mp 112-113°C (alcohol).

PMR spectrum (δ, ppm, J/Hz): 2.36 (3H, s, NCH_3), 2.66 + 2.75 (2H, dd + dd, AB-system, J^1 = 14.0, $ArCH_2$), 2.98 (2H, m, NCH_2), 3.52 (3H, s, OCH_3), 5.86 + 5.87 (2H, s + s, OCH_2O), 6.16 [1H, t, J = 2.4, $C(4)H_{pyraz}$], 6.17 (1H, s, NCHN), 6.37 (1H, s, CH_{arom}), 7.17 [1H, d, J = 2.4, $C(3)H_{pyraz}$], 7.47 [1H, d, J = 2.4, $C(5)H_{pyraz}$].

5-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (3b) was prepared analogously from **1** and 3,5-trimethylpyrazole (**2b**), yield 80%, colorless crystals, mp 121-123°C (not recrystallized).

PMR spectrum (δ, ppm, J/Hz): 2.12 [3H, s, $C(3)_{pyraz}CH_3$], 2.23 [3H, s, $C(5)_{pyraz}CH_3$], 2.34 (3H, s, NCH_3), 2.59 + 2.84 (2H, m + m, AB-system, J^1 = 16.1, $ArCH_2$), 2.92 + 3.58 (2H, m + m, AB-system, NCH_2), 3.48 (3H, s, OCH_3), 5.71 (1H, s, NCH), 5.84 (2H, s, OCH_2O), 5.87 (1H, s, CH_{pyraz}), 6.38 (1H, s, CH_{arom}).

4-Methoxy-6-methyl-5-(3-methyl-1*H*-5-pyrazolylmethyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline (4a). Compound **3b** (1.66 g, 5 mmol) was treated with ethanol (70%, 20 mL), boiled and stirred for 1 h, and cooled. The resulting crystals were separated, washed with alcohol, and dried in air to afford **4a** (1.12 g, 71%) as colorless crystals, mp 166-168°C (alcohol).

PMR spectrum (δ, ppm, J/Hz): 2.33 (3H, s, $C_{pyraz}CH_3$), 2.42 (1H, m, NCH<u>H</u>), 2.45 (3H, s, $N_{piperid}CH_3$), 2.82 (4H, m, $2CH_2$), 3.28 (1H, m, J^1 = 11.4, NC<u>H</u>H), 3.84 (1H, dd, J^1 = 9.6, J^2 = 3.0, NCH), 3.98 (3H, s, OCH_3), 5.23 (1H, s, CH_{pyraz}), 5.81 (1H, br.s, NH), 5.85 (2H, s, OCH_2O), 6.23 (1H, s, CH_{arom}).

1-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)ethan-1-one (6a). A solution of **1** (5 mmol) in CH_3OH (5 mL) was added to a methanolic solution of **5a** (0.69 g, 5 mmol). The resulting solution was held for 1 h at 50°C and left at room temperature for 1 d. The resulting crystals were separated, washed with cold CH_3OH, and dried in air to afford **6a** (1.10 g, 61%) as colorless crystals, mp 158-159°C (alcohol).

PMR spectrum (δ, ppm, J/Hz): 2.39 (3H, s, $C_{pyraz}CH_3$), 2.40 + 2.76 (2H, m + m, AB-system, J^1 = 13.2, $ArCH_2$), 2.49 (3H, s, $N_{piperid}CH_3$), 2.84 + 2.96 (2H, dd + dd, AB-system, J^1 = 15.6, $COCH_2$), 2.86 + 3.09 (2H, m + m, AB-system, J^1 = 12.6, NCH_2), 3.82 (3H, s, $N_{pyraz}CH_3$), 3.93 (3H, s, OCH_3), 4.40 (1H, dd, J^1 = 8.6, J^2 = 3.5, NCH), 5.84 (2H, s, OCH_2O), 6.28 (1H, s, CH_{arom}), 7.75 (1H, s, CH_{pyraz}).

1-(1,3,5-Trimethyl-1*H*-pyrazol-4-yl)-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-ethan-1-one (6b) was prepared analogously from **1** and **5b**, yield 66%, colorless crystals, mp 75-76°C (alcohol).

PMR spectrum (δ, ppm, J/Hz): 2.39 [3H, s, $C(3)_{pyraz}CH_3$], 2.41 [3H, s, $C(5)_{pyraz}CH_3$], 2.42 + 2.74 (2H, m + m, AB-system, J^1 = 13.4, $ArCH_2$), 2.51 (3H, s, $N_{piperid}CH_3$), 2.82 + 3.01 (2H, dd + dd, AB-system, J^1 = 16.1, $COCH_2$), 2.87 + 3.03 (2H, m + m, AB-system, J^1 = 11.1, NCH_2), 3.71 (3H, s, $N_{pyraz}CH_3$), 3.91 (3H, s, OCH_3), 4.49 (1H, dd, J^1 = 8.5, J^2 = 2.6, NCH), 5.84 (2H, s, OCH_2O), 6.28 (1H, s, CH_{arom}).

4-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-1-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)-butan-1,3-dione (8a). A solution of **1** (1.02 g, 4.0 mmol) in CH_3OH (5 mL) was added to a methanolic solution of **7** (0.87 g, 4.5 mmol), held for 1 h at 40°C, left at room temperature for 1 d, treated dropwise with water (15 mL), and cooled to 10°C. The resulting amorphous precipitate was separated and washed with aqueous alcohol. The isolated solid was worked up at 20°C with HCl (1%, 30 mL) with stirring for 2 h. The insoluble solid was separated. The acidic aqueous solution was washed with CCl_4 (15 mL) and made basic with ammonia. The resulting solid was separated, washed with water, recrystallized from the minimal amount of ethanol (60%), and dried in air to afford **8a** (0.92 g, 51%), as light cream-colored crystals, mp 91-92°C.

PMR spectrum (δ, ppm, J/Hz): **8a** (CN): 2.36 [3H, s, $C(3)_{pyraz}CH_3^*$], 2.39 + 2.61 (2H, m + m, AB-system,* $ArCH_2$), 2.44 [3H, s, $C(5)_{pyraz}CH_3$], 2.50 (3H, s, $N_{piperid}CH_3$), 2.66 + 2.88 (2H, m + m, AB-system,* $CO\underline{CH_2}CH$), 2.70 + 3.05 (2H, m + m, AB-system,* NCH_2), 3.71 (3H, s, $N_{pyraz}CH_3^*$), 3.94 (2H, q, AB-system, J^1 = 8.7, $COCH_2CO$), 3.99 (3H, s, OCH_3^*), 4.22 (1H, dd, J^1 = 8.0, NCH), 5.84 (2H, s, OCH_2O), 6.24 (1H, s, CH_{arom}); **8b** + **8c** (EN): 2.36 [3H, s, $C(3)_{pyraz}CH_3^*$], 2.39 + 2.62 (2H, m + m, AB-system,*, $ArCH_2$), 2.43 [3H, s, $C(5)_{pyraz}CH_3$), 2.47 (3H, s, $N_{piperid}CH_3$), 2.64 + 2.85 (2H, m + m, AB-system,* $CO\underline{CH_2}CH$), 2.76 + 3.14 (2H, m + m, AB-system,* NCH_2), 3.72 (3H, s, $N_{pyraz}CH_3^*$), 3.99 (3H, s, OCH_3^*), 4.24 (1H, dd, J^1 = 8.1, NCH), 5.76 (1H, s, =CH), 5.83 (2H, s, OCH_2O), 6.26 (1H, s, CH_{arom}), 16.44 (1H, br.s, OH).

Ethyl-4-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-3-oxobutanoate (11a) was prepared analogously to **8a** from **1** and acetoacetic ester (**10a**) as light yellow-colored crystals, 66% yield, mp 61-62°C ($CHCl_3$:CCl_4).

PMR spectrum (δ, ppm, J/Hz): **11a** (CN): 1.28 (3H, t, J = 7.2, $CH_2\underline{CH_3}$), 2.39 + 2.70 (2H, m + m, AB-system, J^1 = 13.3, $ArCH_2$), 2.41 (3H, s, NCH_3), 2.76 (2H, dd, AB-system, J^1 = 6.4, J^2 = 2.2, $CO\underline{CH_2}CH$), 2.82 + 3.02 (2H, m + m, AB-system, J^1 = 11.6, NCH_2), 3.48 (2H, AB-q, J = 15.2, $COCH_2CO$), 3.97 (3H, s, OCH_3), 4.04 (1H, dd, J^1 = 8.0, NCH), 4.18 (2H, q, J = 7.2, OCH_2), 5.83 (2H, s, OCH_2O), 6.24 (1H, s, CH_{arom}).

4-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)-pentan-2,4-dione (11b) was prepared analogously to **8a** from **1** and actylacetone (**10b**) to give light cream-colored crystals, 76% yield, mp 111-112°C ($CHCl_3$:CCl_4).

PMR spectrum (δ, ppm, J/Hz): **11b** (EN): 2.03 (3H, s, $COCH_3$), 2.35 (3H, s, NCH_3), 2.38 + 3.06 (2H, m + m, AB-system, J^1 = 12.2, NCH_2), 2.44 + 2.52 (2H, m + m, AB-system, J^1 = 13.4, $COCH_2C$=), 2.66 + 2.80 (2H, m + m, AB-system, J^1 = 16.0, $ArCH_2$), 3.99 (3H, s, OCH_3), 4.09 (1H, dd, J^1 = 9.5, J^2 = 3.6, NCH), 5.51 (1H, s, HC=), 5.86 (2H, s, OCH_2O), 6.22 (1H, s, CH_{arom}), 15.55 (1H, br.s, OH); **11b** (CN): 2.16 (3H, s, $COCH_3$), 2.31 (3H, s, NCH_3), 3.57 (2H, AB-q, J = 15.1, $COCH_2CO$), 4.03 (1H, dd, J^1 = 8.6, NCH), remaining signals overlap those of the EN form.

Diethyl-2-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)malonate (12c). A solution of **1** (1.02 g, 4.0 mmol) in $CHCl_3$ (8 mL) was added to a solution of diethylmalonate (**10c**, 0.70 g, 4.4 mmol) in $CHCl_3$ (3 mL), treated with ground anhydrous Na_2SO_4 (1 g), stirred for 1 h at 20°C, and filtered through a paper filter. The desiccant was washed with $CHCl_3$. The combined filtrate was evaporated in vacuo to a volume of 3 mL. The resulting solution was diluted with hexane (15 mL) and cooled to -10°C. The resulting amorphous solid was separated, washed with a small amount of ether, and recrystallized from hexane. Drying in a vacuum desiccator produced **12c** (0.63 g, 40%) as colorless crystals, mp 72-73°C.

PMR spectrum (δ, ppm, J/Hz): 1.15 (3H, t, J = 6.7, CH_3), 1.24 (3H, t, J = 6.7, CH_3), 2.41 (3H, s, NCH_3), 2.58 (2H, m, $ArCH_2$), 2.72 + 3.33 (2H, m + m, AB-system, J^1 = 15.8, NCH_2), 3.66 (1H, d, J = 7.3, OCCHCO), 3.93 (3H, s, OCH_3), 4.48 (1H, d, J = 7.3, NCH), 4.17 (4H, m, J = 6.7, 2×$COOCH_2$), 5.83 (2H, s, OCH_2O), 6.26 (1H, s, CH_{arom}).

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