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SYNTHETIC ENTRY INTO THE SECOISOQUINOLINE ALKALOIDS†

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Abstract Several analogs of secoisoquinoline alkaloids bearing a dimethylaminoethyl side chain and a benzilic, or reduced benzilic group were synthesized. Two independent methods based on the intermediacy of 1,3-dithians and O-benzoylated cyanohydrins as acyl anion equivalents were used.

Recently many secoisoquinoline alkaloids have been isolated. Their characteristic structural feature is a dimethylaminoethyl group derived, probably, *in vivo* from degradation of the nitrogen-containing ring B of transient quaternary tetrahydroisoquinolinium salts. In result of that process a dibenzyl system with different oxidation state of the two central benzylic carbon atoms was formed. Several representative alkaloids of that class are presented in Scheme 1. Bicucullinine **1**[1] and cryptopleurospermine **2**[2] for example, are of benzil construction, N-methylhydrasteine **3**[3] is a desoxybenzoin, while aobamidine **4**[4] and fumaramine **5**[5] can be considered as lactone and lactam, respectively, derived from desoxybenzoin enol.

Secophthalideisoquinolines[6] are the most numerous group in those alkaloids in which a carboxylic function is present either in a free form (e.g. **1**, **3**) or as lactone or lactam (e.g. **4**, **5**). Cryptopleurospermine **2** seems to be by now the only representative of secobenzyloisoquinoline alkaloids with an open B-ring, while peshawarine **6**[7,8] of still lower oxidation state was classified to the so-called secoberbines.[9]

At the outset of our attempts of a total synthesis of the secoisoquinoline alkaloids we have performed some model experiments in order to construct the basic carbon skeleton of alkaloids and to introduce the dimethylaminoethyl side chain. As starting substances in our study aromatic aldehydes were used. Hydrastinine derivatives **7**, **8**[5,10] containing the aminoethyl substituent were substrates for the "upper" part of the molecule and aldehydes **9a–c** became a source of the "lower" part.

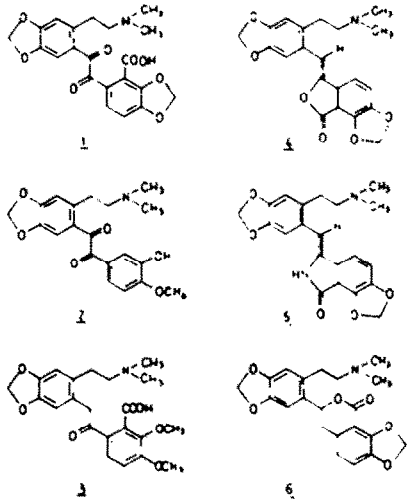
Formation of the C—C bond between the two aldehydes was the key-step of our synthesis. It required the Umpolung of reactivity[11] of one of the aldehydes. For this purpose we have applied two types of masking groups of aldehyde function of **9**. These were: 1,3-dithians **10** and O-benzoylated cyanohydrins **11**. Upon their deprotonation the substances were applied as acyl anion equivalents[12] which easily reacted with the electrophilic aldehyde group of derivatives **7** and **8**.

In this way we have elaborated two parallel methods of synthesis of secoisoquinoline alkaloids.

In the 1,3-dithian method[13] (Scheme 2) thioacetals **10a, b** were deprotonated under the action of n-butyllithium in THF at −76° and treated with a hydrastinine derivative **7**. Thioketals of benzoins **12a, b** were obtained in good yield. Benzoins **16a, b** were isolated upon demasking of the 1,3-dithian group by means of HgO/BF_3.[14] While the reaction was carried out in the presence of air they underwent air-oxidation leading directly to benzils **17a, b**. It was also possible to oxidize benzoins **16** to benzils **17** either with $CuSO_4$/pyridine[15] or with air oxygen.

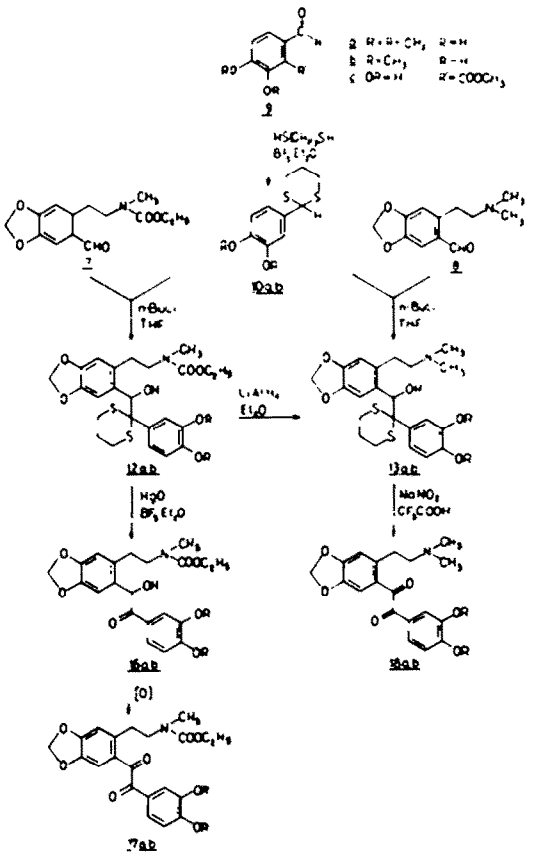
In order to synthesize alkaloid analogs with the N,N-dimethylaminoethyl group the thioketals **12a, b** were reduced with lithium aluminum hydride to amines **13a, b** before hydrolysis of the thioketal function. The same amine **13a** was also obtained from hydrastinine derivative **8** and dithian **10a** under the action of n-butyllithium at −76°. Our attempts at deblocking of the thioketal masking group in amines **13** were met with substantial difficulties. The most satisfying results were reached with the use of the $NaNO_2/CF_3COOH$[16] method, which resulted in formation of final α-diketones **18a, b** instead of the expected α-hydroxy ketones.

In the second method of synthesis O-blocked cyanohydrins were employed as nucleophilic acylating reagents[17] (Scheme 3). A similar approach with the application of O-silylated cyanohydrin was used for the synthesis of cryptopleurospermine **2**, however, no experimental details were disclosed in publication.[18] The reaction of O-benzoyl cyanohydrins **11a, b** with compound **7** was performed in a two-phase catalytic system[19] with triethylbenzylammonium chloride as catalyst. Addition products **14a, b** were formed

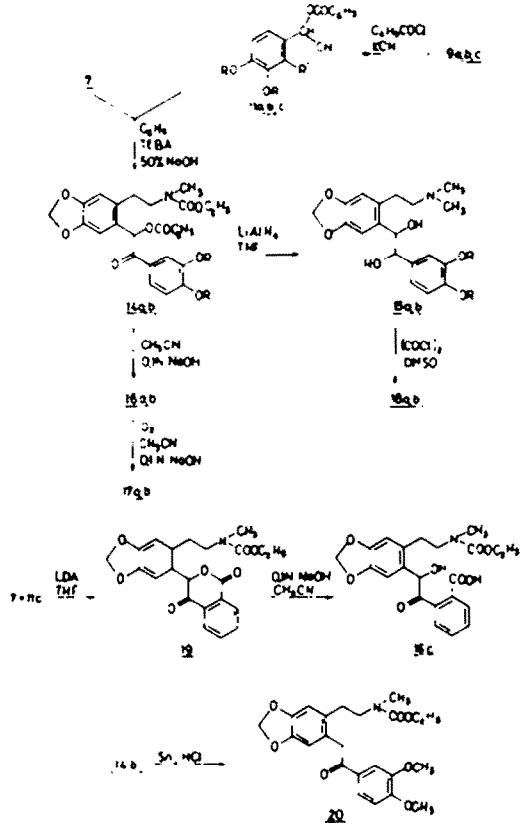


Scheme 1.

† Dedicated to Dr Arnold Brossi on the occasion of his 60th birthday.



Scheme 2.



Scheme 3.

according to our expectation. In case of cyanohydrin of methyl phthalaldehydate **11c**, the reaction required LDA as base and led to δ-lactone **19**. A mild alkaline hydrolysis of those derivatives carried out under the argon atmosphere resulted in benzoins **16a–c** while in the presence of air benzils **17a, b** were obtained, identical with products of the dithian method.

For preparation of alkaloid analogs with the N,N-dimethylaminoethyl moiety, benzoin benzoates **14a, b** were reduced with lithium aluminum hydride to give amino-diols **15a, b**. They could be easily oxidized with DMSO activated with oxalyl chloride[20] leading to final products **18a, b**, identical with benzils synthesized by the previous method.

The synthesized analogs of secoisoquinoline alkaloids exhibit spectral features characteristic of their natural congeneres. The specific N,N-dimethylaminoethyl substituent can be easily detected both by MS and PMR methods. In the mass spectra it gives rise to the most intense peak at 58 *m/e*, derived from $CH_2{=}\overset{+}{N}(CH_3)_2$ fragment ion, suggesting a cleavage of β-bond to the N atom. In PMR spectra the two N-CH_3 groups appear as a sharp six-proton singlet between 2.1 and 2.3 δ.

The bond between the two central benzylic carbon atoms is easily cleaved under electron impact generating two fragment ions corresponding to the "upper" and the "lower" part of molecule, respectively. These peaks can be found in spectra of all compounds with various intensities.

The difference in the oxidation state of the central part of molecules is conveniently demonstrated by their IR spectra. The two benzilic carbonyls exhibit absorption at 1660 and 1605 cm^{-1}, respectively, while benzoins carbonyl appears at *ca* 1690 cm^{-1}.

In both methods employed for the synthesis of secoisoquinoline alkaloids the overall yields are comparable. However, the use of cyanohydrins for nucleophilic acylation appears to be in favour over the 1,3-dithians, because of simpler reaction conditions as well as easier deblocking procedure.

The phthalaldehydic acid derivative was one of the substrates in our synthesis, as shown in Scheme 3. The sequence of reactions: **9c** → **11c** → **19** → **16c** indicates the possibility of introducing carboxylic group as the third function in a molecule.

Besides, we have carried out an experiment in which benzoin benzoate **14b** was reduced by tin in hydrochloric acid giving desoxy benzoin **20**. These above transformations point to the possibility of manipulation of oxidation state within both benzylic positions.

Our study presents a formal total synthesis of secoisoquinoline alkaloids containing the N,N-dimethylaminoethyl group and the dibenzylic system of different oxidation pattern. The use of commercially available aromatic aldehydes and hydrastinine as substrates, seems encouraging for the practical synthesis of many naturally occurring alkaloids of that class.

EXPERIMENTAL

M.ps were determined on a Köffler block and are uncorrected. IR spectra were taken in KBr pellets on a Perkin-

Elmer 180. PMR spectra were recorded on a Tesla BS 467 (60 MHz) in $CDCl_3$ with TMS as internal standard. Mass spectra were taken on a Jeol MS 100 D at 70 eV. Purity of all prepared compounds was checked by TLC on precoated plates (Merck, silica gel 60 F-254). MN silica gel 60 and MN aluminum oxide, neutral, were used for column chromatography.

2-(3,4-Methylenedioxyphenyl)-1,3-dithian (**10a**)

To a well stirred soln of piperonal (3.00 g, 20 mmol) in glacial AcOH (10 ml) 1,3-propanedithiol (3.24 g, 30 mmol) and BF_3·etherate (0.9 g, 6 mmol) were added at ice-bath temp. After 1 hr a crystalline solid was filtered off and washed with cold water (*ca* 2 l). Recrystallization from glacial AcOH yielded 4.47 g (93%) of **10a** as colorless crystals, m.p. 87–88° (lit. 84°[21] and 84.5–85.5°[22]).

2-(3,4-Dimethoxyphenyl)-1,3-dithian (**10b**)

Dithian **10b** was prepared in a similar way as **10a** from veratrum aldehyde (3.32 g, 20 mmol), glacial AcOH (10 ml), 1,3-propanedithiol (3.24 g, 30 mmol) and BF_3·etherate (0.9 g, 6 mmol) with the exception that no ppt appeared after stirring of substrates for 1 hr in ice-bath. The mixture was then rendered alkaline with 15% NaOH and left at 0° overnight. The solid was filtered off, washed with excess of water and recrystallized from ethyl ether. Compound **10b** was obtained in 83% yield (4.25 g), m.p. 83–84° (lit. 99–101°).[23] PMR δ: 2.05 (m, 2H, dithian-CH_2), 2.93 (m, 4H, dithian-CH_2), 3.82 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 5.08 (s, 1H, dithian C_1-H), 6.66–7.05 (m, 3H, Ar-H). MS *m/e* (%): 256 (M^+, 52), 182 (100). (Found: C, 56.33; H, 6.32. Calc for $C_{12}H_{16}O_2S_2$: C, 56.22; H, 6.29%.)

2-Benzoyloxy-2-(3',4'-methylenedioxyphenyl)-acetonitrile (**11a**)

A two-phase system composed of piperonal (3.00 g, 20 mmol) dissolved in benzoyl chloride (3 ml) and KCN (1.95 g, 30 mmol) in water (6 ml) with TEBA (triethylbenzyl ammonium chloride, 0.30 g) was stirred overnight at room temp. The mixture was then extracted with ether, organic phase washed with water, dried and evaporated to give 5.15 g of yellow oil. Two successive crystallizations from 96% EtOH resulted in 4.48 g (80%) of colorless crystals of **11a**, m.p. 51–53° (lit. 57°).[24] IR cm^{-1}: 1725. PMR δ: 6.05 (s, 2H, OCH_2O), 6.65 (s, 1H, C<u>H</u>-CN), 6.85–8.20 (m, 8H, Ar-H). MS *m/e* (%): 281 (M^+, 38), 160 (47), 159 (60), 105 ($C_6H_5CO^+$, 100). (Found: C, 68.23; H, 4.10; N, 4.82. Calc for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98%.)

2-Benzoyloxy-2-(3',4-dimethoxyphenyl)-acetonitrile (**11b**)

Compound **11b** was prepared by the same procedure as **11a**, from veratrum aldehyde (3.32 g, 20 mmol), benzoyl chloride (3 ml), KCN (1.95 g, 30 mmol) and TEBA (0.30 g) with 85% (5.05 g) yield. M.p. 73–75° from 96% EtOH (lit. 61°).[23] IR cm^{-1}: 1735. PMR δ: 3.86 (s, 6H, $ArOCH_3$), 6.58 (s, 1H, C<u>H</u>-CN), 6.75–8.03 (m, 8H, Ar-H). MS *m/e* (%): 297 (M^+, 37), 176 (45), 175 (36), 105 ($C_6H_5CO^+$, 100). (Found: C, 68.64; H, 5.00; N, 4.65. Calc for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71%.)

2-Benzoyloxy-2-(2'-methoxycarbonylphenyl)-acetonitrile (**11c**)

Compound **11c** was prepared from methyl phthalaldehydate (3.00 g, 18.3 mmol), benzoyl chloride (6 ml), KCN (2.4 g, 37 mmol) and TEBA (0.30 g) in the same manner as **11a**, yield 4.85 g (90%) after crystallization from methanol, m.p. 71–72°. IR cm^{-1}: 1740, 1710. PMR δ: 3.87 (s, 3H, $COOCH_3$), 7.33–8.15 (m, 10H, C<u>H</u>–CN and Ar-H). MS *m/e* (%): 295 (M^+, 3), 175 (35), 158 (34), 136 (10), 105 (100). (Found: C, 68.90; H, 4.45; N, 4.69. Calc for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74%.)

2-Hydroxy-2-(2-[β-(N-ethoxycarbonyl-N-methyl)aminoethyl]-4,5-methylenedioxyphenyl)-1-(3,4-methylenedioxyphenyl)-ethanone 1,3-propylenedithioacetal (**12a**)

Thioacetal **10a** (0.96 g, 4 mmol) was dissolved in dry THF (10 ml) under argon. The soln was cooled to −76°, n-BuLi (4.4 mmol) was added dropwise through serum stopper and the temp was raised to −30° and maintained for 1 hr with stirring. The mixture was cooled again to −76° and hydrastinine derivative **7**[5,10] (1.12 g, 4 mmol) in dry THF (4 ml) was introduced. After 1/2 hr the mixture was poured on 20% NH_4Cl and extracted with ether. The neutral fraction obtained on work-up crystallized on treatment with ethyl ether, yielding 1.76 g (85%) of **12a**, m.p. 176–177°. IR cm^{-1}: 3400, 1680. PMR δ: 1.23 (t, J = 7 Hz, 3H, $NCOOCH_2C\underline{H}_3$), 1.96 (m, 2H, dithian-CH_2), 2.83 (s, 3H, NCH_3), 2.25–3.66 (m, 8H, dithian-CH_2 and $ArCH_2CH_2N$), 4.16 (q, J = 7 Hz, 2H, $NCOOC\underline{H}_2CH_3$), 5.21 (s, 1H, ArC<u>H</u>OH), 5.93 (s, 2H, OCH_2O), 6.00 (s, 2H, OCH_2O), 6.53–7.50 (m, 5H, ArH). MS *m/e* (%): 501 (M − H_2O, 5), 280 (97), 239 (100), 116 (22), 44 (7). (Found: C, 57.84; H, 5.43; N, 2.61. Calc for $C_{25}H_{29}NO_7S_2$: C, 57.79; H, 5.62; N, 2.69%.)

2-Hydroxy-1-(3,4-dimethoxyphenyl)-2-(2-[β-(N-ethoxycarbonyl-N-methyl)aminoethyl]-4,5-methylenedioxyphenyl)-ethanone 1,3-propylenedithioacetal (**12b**)

Compound **12b** was prepared from **11b** (0.51 g, 2 mmol), n-BuLi (2.2 mmol) and **7**[5,10] (0.56 g, 2 mmol) in the same manner as described for **12a**. The resulting oil was chromatographed on silica gel (1:10) with benzene–ether (19:1) to give 0.86 g (80%) of amorphous **12b**. IR (film) cm^{-1}: 3430, 1695. PMR δ: 1.16 (t, J = 7 Hz, 3H, $NCOOCH_2C\underline{H}_3$), 2.71 (s, 3H, NCH_3), 1.93–3.26 (m, 10H, dithian-CH_2 and $ArCH_2CH_2N$), 3.65 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 4.03 (q, J = 7 Hz, 2H, $NCOOC\underline{H}_2CH_3$), 5.13 (s, 1H, ArCHOH), 5.83 (s, 2H, OCH_2O), 6.40–7.50 (m, 5H, ArH). MS *m/e* (%): 517 (M − H_2O, 7), 280 (26), 255 (100), 116 (14), 44 (12). (Found: C, 58.46; H, 6.28; N, 2.59. Calc for $C_{26}H_{33}NO_7S_2$: C, 58.30; H, 6.21; N, 2.61%.)

2-Hydroxy-2-(2-[β-(N,N-dimethyl)aminoethyl]-4,5-methylenedioxyphenyl)-1-(3,4-methylenedioxyphenyl)-ethanone 1,3-propylenedithioacetal (**13a**)

1. *From thioketal* **12a**. **12a** (0.86 g, 1.65 mmol) was dissolved in dry ether (215 ml) and $LiAlH_4$ (0.86 g) was added. The mixture was stirred and refluxed for 4 hr, cooled and excess of $LiAlH_4$ was decomposed with 20% NH_4Cl (20 ml). Organic layer was decanted and the inorganic residue was extracted with ether till Dragendorff test was negative. The combined organic extracts were treated with 5% HCl, phases separated and the aqueous layer was basified with 20% NaOH and extracted with ether again. After drying and removal of solvent amine **13a** was obtained in 84% (0.64 g) yield, m.p. 158–159° from anhyd EtOH. IR cm^{-1}: 3100 (broad). PMR δ: 2.11 (s, 6H, NCH_3), 1.66–3.00 (m, 11H, dithiane-CH_2, $ArCH_2CH_2N$ and ArCHOH), 5.10 (s, 1H, ArC<u>H</u>OH), 5.90 (s, 2H, OCH_2O), 5.96 (s, 2H, OCH_2O), 6.50–7.50 (m, 5H, ArH). MS *m/e* (%): 461 (M^+, 7), 222 (35), 165 (7), 58 (100). (Found: C, 59.69; H, 5.94; N, 2.98. Calc for $C_{23}H_{27}NO_5S_2$: C, 59.85; H, 5.90; N, 3.03%.)

In experiments in which the mixture was left overnight at room temp before work-up mixture of products was obtained. After short column chromatography on silica gel (60 HF_{254}, Merck) with $CHCl_3$–MeOH amine **13a** (39%) and diol **15a** (30%) were separated.

2. *From hydrastinine derivative* **8**.[5,10] The procedure applied here was the same as in the case of synthesis of **12a** using **8** (0.42 g, 1.9 mmol) and **10a** (0.46 g, 1.9 mmol). The resulting neutral fraction was extracted with 5% HCl. The acidic aqueous solns were basified with 20% NaOH and extracted with ether to give 0.68 g (77%) of crystalline **13a**, identical with the product of the preceding reaction.

2-Hydroxy-1-(3,4-dimethoxyphenyl)-2-(2-[β-(N,N-dimethyl)aminoethyl]-4,5-methylenedioxyphenyl)-ethanone 1,3-propylenedithioacetal (**13b**)

Compound **13b** was prepared from **12b** (0.39 g, 0.73 mmol) by the $LiAlH_4$ reduction under conditions described for the reduction of **12a**, yield 0.26 g (75%), m.p. 171–172.5° from anhyd EtOH. IR cm^{-1}: 3430 (broad). PMR δ: 2.03 (s, 6H, NCH_3), 1.66–2.93 (m, 11H, dithian-CH_2, $ArCH_2CH_2N$ and ArC<u>H</u>OH), 3.68 (s, 3H, $ArOCH_3$), 3.85 (s, 3H, $ArOCH_3$), 5.07 (s, 1H, ArCHOH), 5.86 (s, 2H, OCH_2O), 6.46–7.56 (m, 5H, ArH). MS *m/e* (%): 477 (M^+, 5), 255 (15), 222 (34), 58 (100).

(Found: C, 60.39; H, 6.52; N, 2.85. Calc for $C_{24}H_{31}NO_5S_2$: C, 60.35; H, 6.54; N, 2.93%.)

2 - *Benzoyloxy* - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - 1 - (3,4 - *methylenedioxyphenyl*) - *ethanone* (**14a**)

To a two-phase catalytic system composed of **11a** (0.84 g, 3 mmol) in benzene (6 ml), 50% NaOH (0.6 ml) and TEBA (0.15 g), **7**[5,10] (0.84 g, 3 mmol) in benzene (6 ml) was added dropwise. The mixture was stirred vigorously under argon at room temp for 1 hr. Water (5 ml) was added, phases separated and the aqueous soln extracted with ether. Combined organic layers were washed with water, dried and evaporated. The oily residue was dissolved in ether and left at 0° overnight. 0.79 g of crystalline **14a** was collected, m.p. 132–134.5°. Additional 0.43 g (total yield 76%) of **14a** was recovered from mother liquors after chromatography on silica gel (1:20) with benzene–ether (9:1). IR cm^{-1}: 1725, 1695. PMR *δ*: 1.18 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.86 (s, 3H, NCH_3), 2.76–3.70 (m, 4H, $ArCH_2CH_2N$), 4.13 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 5.96 (s, 2H, OCH_2O), 6.03 (s, 2H, OCH_2O), 6.73–8.26 (m, 11H, ArH and $ArCHOCOC_6H_5$). MS *m/e* (%): 384 (5), 116 (14), 105 (100), 44 (28). (Found: C, 65.44; H, 5.13; N, 2.63. Calc for $C_{29}H_{27}NO_9$: C, 65.28; H, 5.10; N, 2.62%.)

2 - *Benzoyloxy* - 1 - (3,4 - *dimethoxyphenyl*) - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - *ethanone* (**14b**)

Compound **14b** was prepared from cyanohydrin **11b** (0.89 g, 3 mmol) and **7**[5,10] (0.84 g, 3 mmol) by the same method as used in preparing **14a** with the exception that stirring of substrates was continued for 5 hr. The resulting oily residue was chromatographed on silica gel (1:20) with benzene ether (9:1) to give 1.35 g (82%) of **14b** as foamy white solid which could not be crystallized. IR (film) cm^{-1}: 1715 (shoulder), 1690. PMR *δ*: 1.15 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.80 (s, 3H, NCH_3), 2.73–3.58 (m, 4H, $ArCH_2CH_2N$) 3.83 (s, 6H, $ArOCH_3$), 4.06 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 5.90 (s, 2H, OCH_2O), 6.66–8.16 (m, 11H, ArH and $ArCHOCOC_6H_5$). MS *m/e* (%): 549 (M^+, 0.5), 384 (11), 165 (44), 116 (7), 105 (100), 44 (16). (Found: C, 65.58; H, 5.95; N, 2.55. Calc for $C_{30}H_{31}NO_9$: C, 65.56; H, 5.69; N, 2.55%.)

1 - (2 - [*β* - (N,N - *Dimethyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - 2 - (3,4 - *methylenedioxyphenyl*) - 1,2 - *ethanediol* (**15a**)

Compound **14a** (1.60 g, 3 mmol) was dissolved in dry THF (170 ml) and $LiAlH_4$ (2 g) was added portionwise. The mixture was refluxed with stirring for 4 hr and left overnight at room temp. Excess of $LiAlH_4$ was decomposed with 20% NH_4Cl, organic phase decanted and the inorganic residue was extracted with ether till Dragendorff test was negative. The combined organic extracts were treated with 5% HCl and the acidic layer was reextracted with ether, after being made basic with 20% NaOH. The ethereal soln was dried and evaporated to give 0.79 g (71%) of colorless oil being a mixture of diastereomers of diol **14a**. An analytical sample was recrystallized from benzene, the white solid dried under reduced pressure at water-bath temperature to constant m.p. 135.5–136.5°. IR cm^{-1}: 3330 (broad). PMR *δ*: 2.10 (s, 6H, NCH_3), 2.10–2.83 (m, 4H, $ArCH_2CH_2N$), 3.80 (s, broad, 2H, disappears on treatment with D_2O, OH), 4.66 (s, broad, 2H, ArCHOH), 5.85 (s, 4H, OCH_2O), 6.52–7.00 (m, 5H, ArH). MS *m/e* (%): 373 (M^+, 1), 355 ($M-H_2O$, 4), 222 (5), 58 (100). (Found: C, 64.13; H, 6.24; N, 3.55. Calc for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75%.)

2 - (3,4 - *Dimethoxyphenyl*) - 1 - (2 - [*β* - (N,N - *dimethyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - 1,2 - *ethanediol* (**15b**)

Compound **15b** was prepared by $LiAlH_4$ reduction of **14b** (1.50 g, 2.9 mmol) by the same method as described for the reduction of **14a** with 78% yield (0.88 g), m.p. 113–115°. IR cm^{-1}: 3400 (broad). PMR *δ*: 2.17 (s, 6H, NCH_3), 2.07–2.68 (m, 4H, $ArCH_2CH_2N$), 3.82 (s, 3H, $ArOCH_3$), 3.86 (s, 3H, $ArOCH_3$), 3.98 (s, broad, 2H, disappears on treatment with D_2O, OH), 4.72 (d, J = 8 Hz, 1H, ArCHOH), 4.86 (d, J = 8 Hz, 1H, ArCHOH), 5.90 (s, 2H, OCH_2O), 6.46–7.00 (m, 5H, ArH). MS *m/e* (%): 371 ($M-H_2O$, 2), 222 (7), 58 (100). (Found: C, 64.48; H, 6.90; N, 3.51. Calc for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60%.)

2 - *Hydroxy* - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - 1 - (3,4 - *methylenedioxyphenyl*) - *ethanone* (**16a**)

1. *From dithian* **12a**. To a stirred soln of red HgO (0.39 g, 1.8 mmol) and BF_3 etherate (0.26 g, 1.8 mmol) in 15% aqueous THF (5 ml)[14] a soln of **12a** (0.47 g, 0.9 mmol) in THF (9 ml) was added under argon. After 2 hr the mixture was treated with water (10 ml) and ether (20 ml), phases were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with sat $NaHCO_3$ aq and H_2O, dried and evaporated, yielding 0.30 g of oily residue. It was chromatographed on silicagel (1:10) with benzene–ether (9:1) to give 28 mg (7%) of benzil **17a** and 0.21 g (54%) of benzoin **16a** as colorless crystals, m.p. 138.5–140°. IR cm^{-1}: 3440, 1690, 1670. PMR *δ*: 1.20 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.97 (s, 3H, NCH_3), 3.33–3.80 (m, 4H, $ArCH_2CH_2N$), 4.20 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 4.43 (s, broad, 1H, disappears on treatment with D_2O, OH), 5.95 (s, 2H, OCH_2O), 6.08 (s, 2H, OCH_2O), 6.50 (s, 1H, ArCHOH), 6.80–7.66 (m, 5H, ArH). MS *m/e* (%): 429 (M^+, 9), 280 (55), 206 (100), 149 (45), 116 (23), 44 (67). (Found: C, 61.27; H, 5.43; N, 3.14. Calc for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26%.)

2. *From benzoin benzoate* **14a**. A soln of **14a** (0.53 g, 1 mmol) in acetonitrile (35 ml) and 0.1 N NaOH (20 ml) was refluxed for 1 hr under vigorous stream of argon. Solvent was removed and the residue extracted with ether. Organic extracts were dried, evaporated and the obtained oil was crystallized from 96% EtOH. It deposited 0.23 g of fine crystals of benzoin **16a**. Additional 70 mg of **16a** (total yield 70%) was recovered from mother liquors after chromatography on silica gel (1:10) with benzene ether (9:1).

2 - *Hydroxy* - 1 - (3,4 - *dimethoxyphenyl*) - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - *ethanone* (**16b**)

1. *From dithian* **12b**. Compound **16b** was prepared from **12b** (0.21 g, 0.4 mmol) by the same method as used in preparing **16a** with the exception that the products mixture was chromatographed on silica gel (1:10) with benzene–ether (20:1) to give 28 mg (16%) of **17b** and 96 mg (54%) of amorphous **16b**. IR (film) cm^{-1}: 3430, 1695 (broad). PMR *δ*: 1.21 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.88 (s, 3H, NCH_3), 2.95–3.72 (m, 4H, $ArCH_2CH_2N$), 3.81 (s, 6H, $ArOCH_3$), 4.11 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 4.68 (s, 1H, disappears on treatment with D_2O, OH), 5.82 (s, 2H, OCH_2O), 6.40 (s, 1H, ArCHOH), 6.66–7.43 (m, 5H, ArH). MS *m/e* (%): 445 (M^+, 3), 280 (84), 206 (96), 177 (45), 165 (60), 116 (61), 44 (100). (Found: C, 62.23; H, 6.31; N, 2.97. Calc for $C_{23}H_{27}NO_8$: C, 62.01; H, 6.11; N, 3.14%.)

2. *From benzoin benzoate* **14b**. A mixture consisting of **14b** (0.11 g, 0.2 mmol), acetonitrile (7 ml) and 0.1N NaOH (4 ml) was refluxed under a vigorous stream of argon for 0.5 hr and worked-up in the same way as described for **16a**. Benzoin **16b** (42 mg, 47%) was isolated after column chromatography on silica gel (1:10) with benzene, preceded by **17b** (21 mg, 24%).

2 - *Hydroxy* - 1 - (2 - *carboxyphenyl*) - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - *ethanone* (**16c**)

Compound **16c** was prepared from **19** by the same method as used in preparing **16a, b** from **14a, b**. A mixture of **19** (80 mg, 0.2 mmol), acetonitrile (7 ml) and 0.1 N NaOH (4 ml) was refluxed for 3 hr. Solvent was removed and the residue diluted with water (7 ml) and acidified with 18% HCl. Extraction with ether and the usual work-up yielded **16c** (80 mg, 93%) as yellow

oil. IR (film) cm^{-1}: 3500–2400, 1700, 1670 (broad). PMR δ: 1.23 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.80 (s, 3H, NCH_3), 2.74–3.52 (m, 4H, $ArCH_2CH_2N$), 4.06 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 5.92 (s, 2H, OCH_2O), 6.68 (s, 1H, ArCHOH), 7.45–8.03 (m, 8H, 2H disappear on treatment with D_2O, ArH, OH and COOH). MS *m/e* (%): 411 ($M-H_2O$, 6), 295 (11), 278 (16), 206 (62), 176 (20), 149 (17), 116 (93), 44 (100). (Found: C, 61.22; H, 5.52; N, 3.17. Calc for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26%.)

(2 - [*β* - (N - *Ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*)(3,4 - *methylenedioxyphenyl*) - *ethanedione* (**17a**)

1. *From benzoin* **16a**. To a stirred soln of $CuSO_4 \cdot 5H_2O$ (50 mg, 0.2 mmol), pyridine (0.3 ml) and water (0.12 ml)[15] **16a** (43 mg, 0.1 mmol) was added at 60°. The mixture was stirred for 2 hr, cooled, water (5 ml) was added and left overnight at 0°. The soln was decanted and the remaining yellow oil was dissolved in ether, dried and concentrated to deposit 30 mg (60%) of yellow crystals of **17a**, m.p. 102.5–104°. IR cm^{-1}: 1695, 1660 and 1605. PMR δ: 1.22 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.95 (s, 3H, NCH_3), 3.38–3.63 (m, 4H, $ArCH_2CH_2N$), 4.12 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 6.01 (s, 2H, OCH_2O), 6.08 (s, 2H, OCH_2O), 6.91–7.53 (m, 5H, ArH). MS *m/e* (%): 427 (M^+, 1), 278 (43), 206 (100), 149 (49), 116 (33), 44 (61). (Found: C, 61.67; H, 5.02; N, 3.19. Calc for $C_{22}H_{21}NO_8$: C, 61.82; H, 4.95; N, 3.28%.)

2. *From benzoin benzoate* **14a**. A soln of **14a** (107 mg, 0.2 mmol) in acetonitrile (7 ml) and 0.1 N NaOH (4 ml) was stirred for 48 hr at room temp. Solvent was removed, the residue extracted with ether, dried and evaporated. The resulting yellow oil was crystallized from ethyl ether giving 58 mg (68%) of yellow crystals of **17a**.

(3,4 - *Dimethoxyphenyl*)(2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - *ethanedione* (**17b**)

1. *From benzoin* **16b**. Compound **16b** (83 mg, 0.18 mmol) in acetonitrile (6 ml) and 0.1 N NaOH (2 ml) were stirred for 24 hr at room temp. Solvent was evaporated and the residue extracted with ether. Organic phase was dried and evaporated to give 58 mg (72%) of **17b** as yellow solid, which crystallized from anhyd EtOH. An analytical sample was prepared by drying under vacuum at water-bath temp to constant m.p. 100–103°. IR cm^{-1}: 3450 (water of crystallization), 1705, 1660 and 1605. PMR δ: 1.20 (t, J = 7 Hz, 3H, $NCOOCH_2CH_3$), 2.92 (s, 3H, NCH_3), 3.00–3.65 (m, 4H, $ArCH_2CH_2N$), 3.93 (s, 6H, $ArOCH_3$), 4.10 (q, J = 7 Hz, 2H, $NCOOCH_2CH_3$), 6.00 (s, 2H, OCH_2O), 6.73–7.65 (m, 5H, ArH). MS *m/e* (%): 443 (M^+, 2), 278 (42), 206 (100), 165 (91), 116 (19), 44 (8). (Found: C, 61.43; H, 5.47; N, 3.06. Calc for $C_{23}H_{25}NO_8 \cdot 1/4H_2O$: C, 61.67; H, 5.74; N, 3.13%.)

2. *From benzoin benzoate* **14b**. Compound **14b** (250 mg, 0.46 mmol) in acetonitrile (16 ml) and 0.1 N NaOH (9 ml) were refluxed for 9 hr. After evaporation of solvent the residue was extracted with ether washed with water, dried and evaporated. The yellow residue was crystallized from anhydrous ethanol to give 125 mg (61%) of benzil **17b**.

(2 - [*β* - (N,N - *Dimethyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*)(3,4 - *methylenedioxyphenyl*) - *ethanedione* (**18a**)

1. *From dithian* **13a**. To a soln of **13a** (203 mg, 0.44 mmol) in CF_3COOH (0.7 ml) and water (0.15 ml) $NaNO_2$ (2.7 mg, 0.04 mmol) was added.[16] The mixture was stirred for 40 min, then water (5 ml) was added and the mixture rendered alkaline with 15% KOH. It was extracted with ether till Dragendorff test was negative. After drying and removal of solvents the resulting yellow oil was chromatographed on 2° aluminum oxide (1 : 10) with benzene to give 102 mg (63%) of pure **18a** as yellow oil which could be neither crystallized nor distilled. IR (film) cm^{-1}: 1665 and 1605. PMR δ: 2.26 (s, 6H, NCH_3), 2.56 (m, 2H, $ArCH_2CH_2N$), 3.22 (m, 2H, $ArCH_2CH_2N$), 5.93 (s, 2H, OCH_2O), 6.00 (s, 2H, OCH_2O), 6.70–7.46 (m, 5H, ArH). MS *m/e* (%): 369 (M^+, 1), 220 (2), 149 (6), 58 (100). (Found: C, 64.89; H, 5.50; N, 3.56. Calc for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79.) Perchlorate salt of **18a**: yellow needles, m.p. 187° (dec). (Found: C, 50.95; H, 4.08; N, 2.99. Calc for $C_{20}H_{19}NO_6 \cdot HClO_4$: C, 51.13; H, 4.29; N, 2.98%.)

2. *From diol* **15a**. A stirred soln of oxalyl chloride (0.23 g, 1.8 mmol) in dry methylene chloride (4 ml) was cooled to −60° and DMSO (0.37 g, 4.8 mmol) in dry methylene chloride (1 ml)[20] was added dropwise. Stirring was continued at −60° for 10 min then **15a** (0.37 g, 1 mmol) in methylene chloride (2 ml) was introduced dropwise. The mixture was stirred for 15 min and triethylamine (1.00 g, 10 mmol) was added with stirring at −60°. The cooling bath was removed and water (6 ml) was added at room temp. Stirring was continued for 10 min and organic layers were separated. The aqueous phase was extracted with methylene chloride, the combined organic solns were dried and evaporated to give 0.23 g of alkaline fraction, which was chromatographed on 2° aluminum oxide (1 : 10) with benzene–ether (9 : 1). Benzil **18a** was obtained with 47% (0.17 g) of yield.

(3,4 - *Dimethoxyphenyl*)(2 - [*β* - (N,N - *dimethyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl* - *ethanedione* (**18b**)

1. *From dithian* **13b**. Compound **18b** was prepared from **13b** (143 mg, 0.3 mmol) by the same method as used in preparing **18a**, yield 60 mg (52%) m.p. 88–91°, yellow needles from ether. IR cm^{-1}: 3430 (water of crystallization), 1660 and 1605. PMR δ: 2.27 (s, 6H, NCH_3), 2.10–3.42 (m, 4H, $ArCH_2CH_2N$), 3.86 (s, 6H, $ArOCH_3$), 5.91 (s, 2H, OCH_2O), 6.63 (s, broad, 1H, disappears on treatment with D_2O, water of crystallization), 6.77–7.51 (m, 5H, ArH). MS *m/e* (%): 385 (M^+, 2), 220 (2), 165 (5), 58 (100). (Found: C, 63.79; H, 5.91; N, 3.55. Calc for $C_{21}H_{23}NO_6 \cdot 1/2H_2O$: C, 63.95; H, 6.13; N, 3.55%.)

2. *From diol* **15b**. Diol **15b** (304 mg, 0.8 mmol) was oxidized with DMSO–oxalyl chloride in the same way as diol **15a**, leading to benzil **18b** (290 mg, 94%) as yellow crystals.

3 - (2' - [*β* - (N - *Ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4',5' - *methylenedioxyphenyl*)*isochroman* - 1,4 - *dione* (**19**)

n-BuLi (1.1 mmol) was added dropwise to a soln of diisopropylamine (0.10 g, 1 mmol) in dry THF (4 ml) at 0° under argon. The soln was cooled to −70° and **11c** (0.29 g, 1 mmol) in THF (2 ml) was introduced dropwise yielding a dark red soln. The temp was maintained at −70° for 1/2 hr, then allowed to rise to −40° and 7[5,10] (0.28 g, 1 mmol) in THF (1 ml) was added dropwise. The mixture was kept at −40° for 1 hr then brought to room temp, poured on 20% NH_4Cl and extracted with ether. The organic phase was dried, evaporated and the resulting oil (0.55 g) crystallized on treatment with ethyl ether. Digestion with MeOH yielding 0.15 g (36%) of **19** as a very unstable crystalline solid, m.p. 185–187°. IR cm^{-1}: 1720, 1675 and 1650. PMR δ: 1.98 (m, 3H, $NCOOCH_2CH_3$), 2.50 (s, 3H, NCH_3), 2.47–3.80 (m, 6H, $ArCH_2CH_2N$ and $NCOOCH_2CH_3$), 6.06 (s, 2H, OCH_2O), 6.92 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.45–8.25 (m, 4H, ArH). MS *m/e* (%): 411 (M^+, 20), 295 (22), 176 (14), 163 (11), 149 (25), 132 (7), 116 (100), 44 (96). (Found: C, 63.97; H, 5.50; N, 3.50. Calc for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15; N, 3.40%.)

1 - (3,4 - *Dimethoxyphenyl*) - 2 - (2 - [*β* - (N - *ethoxycarbonyl* - N - *methyl*)*aminoethyl*] - 4,5 - *methylenedioxyphenyl*) - *ethanone* (**20**)

Benzoin benzoate **14b** (0.18 g, 0.33 mmol) dissolved in 96% EtOH (5 ml) was treated with conc HCl (0.24 ml), Sn (0.12 g) and catalytic amounts of $CuSO_4 \cdot 5H_2O$. The mixture was refluxed for 5 hr, left overnight with stirring at room temp, then conc HCl (0.15 ml) and tin (80 mg) added again and refluxed for 9 hr and left overnight. EtOH was evaporated and the residue extracted with ether. The ethereal extracts were washed with 1% NaOH, water, dried and evaporated to give 80 mg (57%) of crystalline **20**, m.p. 106–108° from MeOH. IR cm^{-1}: 1695 (broad). PMR δ: 1.20 (m, 3H, $NCOOCH_2CH_3$), 2.83 (s, 3H, NCH_3), 2.62–3.43 (m, 4H, $ArCH_2CH_2N$), 3.93 (s, 3H, $ArOCH_3$), 3.95 (s, 3H, $ArOCH_3$), 3.90–4.10 (m, 2H, $NCOOCH_2$

CH_3), 4.26 (s, 2H, $ArC\underline{H}_2$), 5.90 (s, 2H, OCH_2O), 6.63–6.95 (m, 3H, ArH), 7.58 7.73 (m, 2H, ArH). MS *m/e* (%): 429 (M^+, 6), 411 (18), 264 (2), 165 (100), 116 (38), 44 (58). (Found: C, 64.35; H, 6.25; N, 3.15. Calc for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26%.)

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REFERENCES

[1] R. G. A. Rodrigo, R. H. F. Manske, H. L. Holland, D. B. MacLean, *Can. J. Chem.* **54**, 471 (1976).
[2] S. R. Johns, J. A. Lamberton, A. A. Sioumis, R. J. Willing, *Aust. J. Chem.* **23**, 353 (1970).
[3] P. Foragacs, J. Provost, R. Tiberghieu, J.-F. Desconclois, G. Bufard, M. Pesson, *C.R. Acad. Sci., Paris Ser. D* **276**, 105 (1973).
[4] T. Kametani, M. Takemura, M. Ihara, K. Fukumoto, *J. Chem. Soc. Perkin Trans. I* 390 (1977).
[5] S. F. Hussain, M. Shamma, *Tetrahedron Lett.* **21**, 1693 (1980).
[6] G. Blasko, V. Elango, B. Sener, A. J. Freyer, M. Shamma, *J. Org. Chem.* **47**, 880 (1982).
[7] M. Shamma, A. S. Rothenberg, G. S. Jayatilake, S. F. Hussain, *Heterocycles* **5**, 41 (1976).
[8] M. Shamma, A. S. Rothenberg, S. F. Hussain, *Heterocycles* **6**, 707 (1977).
[9] M. Shamma, A. S. Rothenberg, G. S. Jayatilake, S. F. Hussain, *Tetrahedron* **34**, 635 (1978).
[10] M. D. Rozwadowska, *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **19**, 673 (1971).
[11] D. Seebach, *Angew. Chem.* **18**, 239 (1979).
[12] O. W. Lever, *Tetrahedron* **32**, 1943 (1976).
[13] D. Seebach, E. J. Corey, *J. Org. Chem.* **40**, 231 (1975).
[14] E. Vedejs, P. L. Fuchs, *J. Org. Chem.* **36**, 366 (1971).
[15] H. T. Clarke, F. F. Dreger, *Org. Synth. Coll. Vol.* **1**, 87 (1941).
[16] G. A. Olah, S. C. Narang, G. F. Salem, B. G. B. Gupta, *Synthesis* 273 (1979).
[17] J. D. Albright, *Tetrahedron* **39**, 3207 (1983).
[18] G. C. Dunmore, R. H. Manske, R. Rodrigo, *Heterocycles* **8**, 391 (1977).
[19] M. Makosza, *Surv. Prog. Chem.* **9**, 1 (1980).
[20] K. Omura, D. Swern, *Tetrahedron* **34**, 1651 (1978).
[21] A. G. Gonzalez, J. P. Perez, J. M. Trujillo, *Tetrahedron* **34**, 1011 (1978).
[22] D. Seebach, H. F. Leitz, V. Ehrig, *Chem. Ber.* **108**, 1924 (1975).
[23] H. Ramuz, *Arzneim.-Forsch.* **28**, 2048 (1978).
[24] *Beilsteins Handbuch der Organischen Chemie*, Vol. 19, p. 295. Verlag von Julius Springer, Berlin (1934).
[25] *Beilsteins Handbuch der Organischen Chemie*, Drittes Ergänzungswek, Vol. 10, p. 2104. Springer Verlag, Berlin, Heidelberg, New York (1971).