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# Syntheses and Biological Activities of 1,4-Disubstituted Piperidines[1)]

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The 1,4-substituted piperidines **16–22** have been synthesized from the 1-substituted 4-piperidones **5** and **6**. The antiamoebic, antileishmanial and anticancer activities of these compounds are described.

**Synthese und biologische Aktivität 1,4-disubstituierter Piperidine**

Die 1,4-substituierten Piperidine **16–22** wurden ausgehend von den 1-substituierten 4-Piperidonen **5** und **6** synthetisiert. Die Aktivitäten dieser Verbindungen gegenüber Amoeben, Leishmanien und lymphatischer Leukämie werden beschrieben.

Emetine **(1)** is still one of important drugs for the treatment of chronic amoebiasis, particularly hepatic amoebiasis[2,3)]. It also possesses *in vitro* antileishmanial activity against the promastigate stages and has also been found effective in the treatment of cutaneous leishmaniasis[4,5)] and non-specific granulomas[6)] (tumors). Its wider clinical use is limited due to its cardiotoxic action[7)]. The structure activity relationship studies for various emetine analogs reveal that the presence of the ethyl group at C-3 is not an essential requirement for antiamoebic activity because (±) noremetine **(2)** having a

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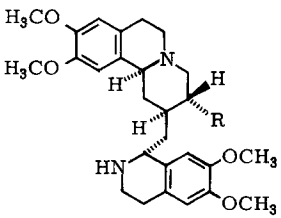
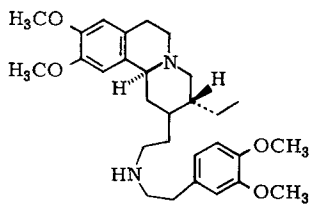
methyl group at C-3 and (±) bisnoremetine **(3)** devoid of any substituent at C-3 retain *in vivo* amoebicidal activity[8]. Among various secoanalogs 1′,8′a-seco-emetine **(4)** has modest *in vivo*[8] antiamoebic activity. In view of these results and to gain more insight into the minimal structural requirements for activity, it appeared of interest to synthesise the 1-benzyl- or 1-methyl-4-(2-substituted-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)piperidines **16, 17, 20, 22** and the 1-benzyl- or 1-methyl-4-[β-(3,4-dimethoxyphenyl)ethyl]ethylaminoethylpiperidines **18** and **19**, which may be considered as 1′,8′ a-seco-analogs of **16** and **17**. The synthesis of these compounds, their *in vitro* antiamoebic, and antileishmanial and anticancer activities are reported in this communication.

1-Benzyl-4-piperidone **(5)** was condensed with triethyl phosphonoacetate in presence of sodium hydride in dry 1,2-dimethoxyethane, when a 1:1 mixture of 4-ethoxycarbonylmethylene-1-benzylpiperidine **(7a)** and ethyl 1-benzyl-1,2,5,6-tetrahydropyridyl-4-acetate **(7b)** was formed as shown by one sharp resonance signal at $\delta = 5.46$ ppm presumably for the exocyclic olefinic proton of **7a** and a triplet at $\delta = 5.34$ ppm for the endocyclic olefinic proton of **7b**; the PMR showed other expected signals such as singlets at $\delta = 3.52$ and $\delta = 3.45$ ppm for N-$\underline{CH_2}$-$C_6H_5$ confirming the formation of the two isomers. Catalytic hydrogenation of this mixture over Pd/C in ethanolic HCl gave ethyl piperidyl-4-acetate **(10)** while hydrogenation over Pt in ethanol afforded the required ethyl 1-benzylpiperidyl-4-acetate **(9)**. The ester **9** on heating with 3,4-dimethoxyphenethylamine gave 1-benzyl-4-(3,4-dimethoxyphenethylcarbamoylmethyl)piperidine **(12)** which on *Bischler-Napieralski* cyclisation with $POCl_3$ in benzene followed by reduction with sodium borohydride in methanol yielded the 1-benzyl-4-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)piperidine **16. 16** should exist as a racemate due to the generation of an asymmetric centre at C-1, attempts to resolve the racemate into its enantiomers similar to the method used in the resolution of (±) emetine[9] were unsuccessful. In order to verify the possible existence of the two rotamers around the -N-CO-bond, the N-2′-acetyl derivative **20** and the N-2′-benzoyl derivative **21** were prepared by treating **16** with acetylchloride and benzoyl chloride in presence of triethylamine (Scheme 1). In the PMR

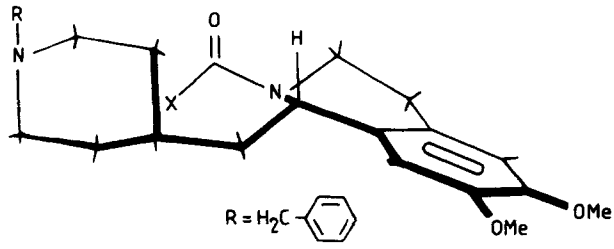


**1**: R = $C_2H_5$
**2**: R = $CH_3$
**3**: R = H

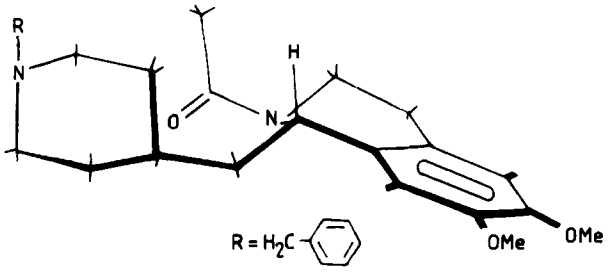


**4**

spectrum of the acetylated derivative **20**, H-1′ appeared downfield at $\delta = 4.72$ and $\delta = 5.64$ ppm, each integrating for 0.5 H. The appearance of the two signals for H-1′ at relatively downfield might either be due to the existence of two average rotamers (Fig. 1)




Rotamer **A**

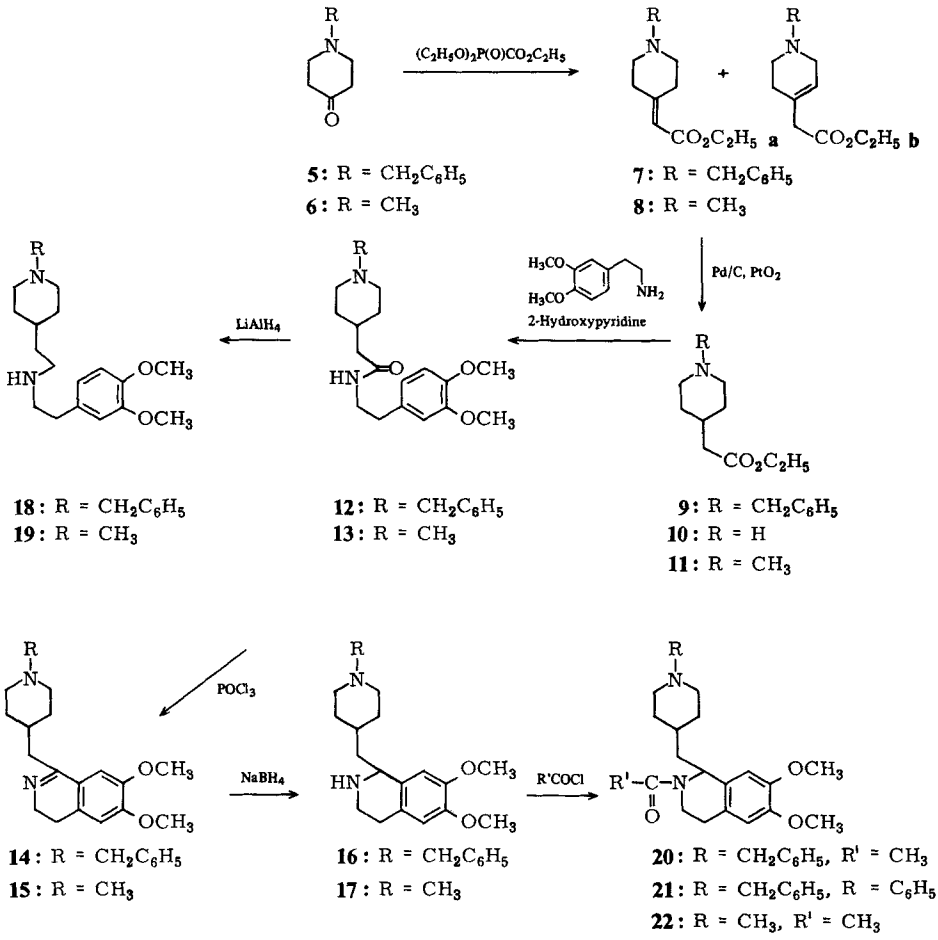



Ph 643.1

Rotamer **B**

on account of the restricted rotation around -N-CO-bond. The existence of two rotamers was supported by $^{13}$CNMR spectra at 25° and −40° where the aromatic C-6′ and C-7′ carbon appeared together at δ = 148.03 ppm at 25° and in the low temp. spectrum (−40°) they appeared at δ = 146.80 and δ = 147.20 ppm. Similarly the carbonyl carbon appearing at δ = 169.19 ppm at 25° splitted in two signals at δ = 169.38 and δ = 169.51 ppm at low temperature (−40°) in $^{13}$CMNR spectra. The low field signal at δ = 5.64 ppm in PMR should correspond to H-1′ in rotamer **A** falling in the deshielding cone of C=O while the signal at δ = 4.72 ppm should correspond to the H-1′ in the rotamer **B** where H-1′ does not fall under the deshielding cone of C=O. The fact was also supported by the shift reagent (Eu(fod)$_3$) added PMR spectrum of **20** in which the shift of H-1′ in rotamer **A** was more as compared to that in other rotamer **B**. Further in the shift reagent added PMR spectrum the singlet for 6′,7′-$OCH_3$ protons was splitted into two singlets which might be due to the puckering of ring B of tetrahydroisoquinoline in which $COCH_3$ falls near to the -$OCH_3$ of ring A.

The corresponding 1-methyl-4-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)piperidine **(17)** was synthesized similarly from 1-methyl-4-piperidone **(6)**. In this case, unlike in the reaction of **5** with triethylphosphonoacetate, the two isomers **8a** and **8b** were formed in a ratio of 2:1 as revealed by the integration of the singlet at δ = 5.52 and the triplet at δ = 5.42 ppm and also by other resonance signals such as a quartet at δ = 4.02 and δ = 4.00 ppm for 2-protons of -$OCH_2$, two singlets at δ = 2.28 and δ = 2.18 ppm for 3-protons of N-$CH_3$, two triplets at δ = 1.18 and δ = 1.15 ppm for 3-protons of -$COOCH_2\underline{CH_3}$. The mixture was converted to 1-methyl-4-(2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)-piperidine **(22)**, similar to **20** by its reduction,




condensation with β-(3,4-dimethoxyphenyl)ethylamine followed by *Bischler-Napieralski* cyclisation, reduction and acetylation.

Lithium aluminium hydride reduction of the amides **12** and **13** yielded the 1-benzyl- or 1-methyl-4[β-(3,4-dimethoxyphenyl)ethyl]aminoethylpiperidines **18** and **19** as 1′,8′ a-seco-analogs of **16** and **17**.

## Antiamoebic activity

The compounds **7–17, 19–21** were tested *in vitro* for their antiamoebic activity against *E. histolytica.* (NIH-200)[10] strain in axenic culture. Most of the compounds did not show marked antiamoebic activity upto a concentration of 125 μg/ml while **8** was active at 125 μg/ml. Metronidazole and emetine HCl were used as standard drugs to run as control and these were active at 8 μg/ml.

**Antileishmanial activity**

The compounds **8, 16, 17, 20** and **21** were tested for their antileishmanial activity against promastigote of a strain of *L. donavani* grown in culture for 5–6 days[11]. Among these compounds **8** and **20** were active at 800 μg, **16** and **21** were active at 50 μg and 200 μg while **17** was inactive upto a dose of 800 μg against standards like emetine and dehydroemetine which were active at 16μg and 8 μg.

**Anticancer activity**

The compounds **12, 13** and **16** were tested for their anticancer activity against lymphoid leukemia PS 388 under the Cancer Chemotherapy Programme at the Nation Institutes of Health, Bethesda, Maryland, USA. These compounds were inactive as shown by their T/C ratio being 120.

The authors thank to Drs. *S. R. Das* and *G. P. Dutta* for antiamoebic and antileishmanial results. Grateful acknowledgements to NIH, Bethesda, Maryland, USA, for anticancer screening results. One of us (KAG) thanks the University Grants Commission, New Delhi, for awarding a teacher research fellowship.

## Experimental Part

*IR:* Perkin-Elmer 157 and 177 infracord spectrophotometers. *PMR:* Varian A–60D and R–32 spectrophotometers, TMS int. ref. *MS:* Jeol-J MS D–300. The purity of the compounds was checked on silica gel G-plates and spots were located by iodine vapours or $KMnO_4$ spray. *MP:* in sulphuric acid bath, uncorr. The analyses of the compounds are tabulated in table 1.

**Table 1:** *Compounds* **7–22**

| Compound | Molecular formula | | Calcd. | | | Found | | |
|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | C | H | N |
| 7 | $C_{16}H_{21}NO_2$ | (259) | 74.1 | 8.10 | 5.4 | 74.0 | 8.37 | 5.9 |
| 8 | $C_{10}H_{17}NO_2$ | (183) | 65.6 | 9.28 | 7.6 | 65.8 | 9.53 | 7.5 |
| 9 | $C_{16}H_{23}NO_2$ | (261) | 73.6 | 8.81 | 5.4 | 73.9 | 8.65 | 5.2 |
| 10 | $C_9H_{17}NO_2$ | (171) | 63.2 | 9.94 | 8.2 | 63.7 | 10.08 | 7.9 |
| 11 | $C_{10}H_{19}NO_2$ | (185) | 64.8 | 10.27 | 7.6 | 65.0 | 10.82 | 7.9 |
| 12 | $C_{24}H_{32}N_2O_3$ | (396) | 72.7 | 8.08 | 7.1 | 73.0 | 8.25 | 7.3 |
| 13 | $C_{18}H_{28}N_2O_3$ | (320) | 67.5 | 8.75 | 8.8 | 67.1 | 8.33 | 8.3 |
| 14 | $C_{24}H_{30}N_2O_2$ | (378) | 76.2 | 7.93 | 7.4 | 76.7 | 8.27 | 7.0 |
| 15 | $C_{18}H_{26}N_2O_2$ | (302) | 71.5 | 8.62 | 9.3 | 71.8 | 8.82 | 9.8 |
| 16 | $C_{24}H_{32}N_2O_2$ | (380) | 75.8 | 8.42 | 7.4 | 76.2 | 8.52 | 7.8 |
| 17 | $C_{18}H_{28}N_2O_2$ 2HBr · $H_2O$ | (482) | 44.8 | 6.64 | 5.8 | 45.1 | 6.86 | 5.8 |
| 18 | $C_{24}H_{34}N_2O_2$ | (382) | – | – | 7.3 | – | – | 7.8 |
| 19 | $C_{18}H_{30}N_2O_2$ | (306) | 70.6 | 9.80 | 9.2 | 70.6 | 10.02 | 8.8 |
| 20 | $C_{26}H_{34}N_2O_3$ | (422) | 73.9 | 8.06 | 8.6 | 74.1 | 8.43 | 6.0 |
| 21 | $C_{31}H_{36}N_2O_3$ | (484) | 76.9 | 7.44 | 5.8 | 77.0 | 7.44 | 5.2 |
| 22 | $C_{20}H_{30}N_2O_3$ | (346) | 69.4 | 8.67 | 8.1 | 69.5 | 8.52 | 8.2 |

*1-Benzyl-4-ethoxycarbonylmethylene-piperidine* (**7a**) *and ethyl-1-benzyl-1,2,5,6-tetrahydropyridyl-4-acetate* (**7b**)

A solution of 22.4 g (0.1 mol) triethyl phosphonoacetate in 20 ml dry 1,2-dimethoxyethane was added dropwise to a stirred suspension of 6.0 g of 50 % oil dispersion (0.125 mol) sodium hydride in 120 ml dry 1.2-dimethoxyethane at 0°C. The stirring was continued for 30 min and thereafter a solution of 18.9 g (0.1 mol) **5** in 5 ml dry 1,2-dimethoxyethane was added dropwise at 10°C. The reaction mixture was stirred at 30°C for 2 h and was diluted with 350 ml water and the separated oil extracted with 3 × 200 ml ether. The ether extracts were extracted with 50 ml 1N-HCl. The acidic layer was basified with 50 ml 1 N–NaOH and extracted with ether, dried ($Na_2SO_4$) and concentrated to get a pure compound as oil, yield 21.0 g (80 %). IR (Neat): 2820 ($CH_2$), 1740 (CO), 1725 (CO), 1660 $cm^{-1}$ (C=C). PMR ($CCl_4$): δ (ppm) = 1.5 (t, 3, $CH_3$), 1.9–3.0 (m, 8, =C–$CH_2$, $NCH_2$), 3.45 and 3.52 (two s, 2, Ar–$NCH_2$), 5,34 (t, 0.5, =C–$CH_2$), 5.45 (s, 0.5, COCH=), 7.1 (s, 5, Ar-H). Similarly **8a** and **8b** were prepared from **6**; yield 75 %, $b.p._9$ 102–106°. IR (Neat): 1730 (–CO), 1718 (–CO), 1655 $cm^{-1}$ (C=C); PMR ($CCl_4$): δ (ppm) = 1.15 and 1.18 (2t, 3, $-OCH_2-CH_3$), 2.18 and 2.23 (2s, 3, $-NCH_3$), 2.25–3.05 (m, 8, $-CH_2$), 5.4 (t, 0.33, = CH–$CH_2$–N), 5.52 (s, 0.67, –C=CH–CO).

*Ethyl 1-benzyl-piperidyl-4-acetate* (**9**)

A mixture of 7.78 g (0.03 mol) **7a** and **7b**, 0.8 g $PtO_2$ and 80 ml ethanol was hydrogenated at 50 psi of hydrogen for 4 h. The catalyst was filtered and solvent was removed to get pure compound **9** as colourless oil, yield 7.3 g (93 %). IR (Neat): 1725 $cm^{-1}$ (CO); PMR ($CCl_4$): δ (ppm) = 1.0–3.2 (m, 14, aliphatic-H), 3.33 (s, 2, Ar-$NCH_2$), 3.95 (q, 2, $-OCH_2$), 7.08 (s, 5, Ar-H).

*Ethyl pyridyl-4-acetate* (**10**)

A mixture of 5.18 g (0.02 mol) **7a** and **7b**, 4.4 ml (20 % v/v) ethanolic HCl, 1.0 g (10 %) Pd/C and 20 ml ethanol was hydrogenated at 50 psi of $H_2$ for 4 h. The catalyst was filtered, washed with ethanol, the filtrate was concentrated, basified with $Na_2CO_3$ solution and extracted with ether, dried ($Na_2SO_4$) and solvent was removed to give **10** as colourless oil, yield 2.7 g: IR (Neat): 3350 (NH), 1730 (–CO) $cm^{-1}$; PMR ($CCl_4$): δ (ppm) = 0.95–3.4 (m, 14, aliphatic-H), 3.98 (q, 2, $-OCH_2$), 4.24 (bs, 1H, NH).

In similar manner **11** was prepared from a mixture of **8a** and **8b**, yield 88.5 % IR (Neat): 1730 $cm^{-1}$ (CO); PMR ($CCl_4$): δ (ppm) = 1.05–3.10 (m, 14, aliphatic H), 2.16 (s, 3, $-NCH_3$), 3.98 (q, 2, $-OCH_2$).

*1-Benzyl-4-(3,4-dimethoxypheneythylcarbamoylmethyl)piperidine* (**12**)

A mixture of 5.24 g (0.24 mol) **9** and 8.68 (0.48 mol) 3,4-dimethoxyphenylethylamine in 1.44 g (0.015 mol) 2-hydroxypyridine was heated under nitrogen atmosphere at 170°C for 8 h. The reaction mixture was then cooled to 100°C and stirred with 80 ml ether for 30 min, cooled to 30°C and again stirred with 80 ml ether. The ether layer was separated and crystallised solid was filtered to give **12**, yield 6.77 g (86 %), m.p. 102°C. IR (KBr): 3330 (NH), 2920 (arom.), 2820 ($CH_2$), 1650 $cm^{-1}$ (NCO); PMR ($CDCl_3$): δ (ppm) = 1.01–2.1 (m, 9, CH, $CH_2$, Ar-$CH_2$), 2.5–2.9 (m, 4, $NCH_2$), 3.2–3.5 (m, 4, –N–$CH_2$–Ar, $CONCH_2$), 3.75 (s, 6, $-OCH_3$), 5.57 (bs, 1, –NH), 6.5–6.8 (m, 3, Ar–H), 7.18 (m, 5, $-CH_2-C_6H_5$): MS: m/e = 396.

Similarly **13** was prepared from **11**, yield 77 %, m.p. 84–86°C. IR (KBr): 3340 (NH), 2950 (arom.), 1645 $cm^{-1}$ (NCO); PMR ($CDCl_3$): δ (ppm) = 1.0–2.05 (m, 7, –CH, $-CH_2$), 2.3–3.0 (m, 6, $-NCH_2$, Ar–$CH_2$), 3.4 (q, 2, $-CHNCH_2$), 3.76 (s, 6, $-OCH_3$), 5.8 (bs, 1, –NH), 6.45–6.58 (m, 3, Ar–H); MS: m/e = 320.

*1-Benzyl-4-(6,7-dimethoxy-3,4-dihydro-1-isoquinolylmethyl)piperidine* **(14)**

A mixture of 1.98 g (5 mmol) **12**, 4 ml $POCl_3$ in 50 ml dry benzene was refluxed for 1.5 h and cooled. The benzene layer was decanted and the residue was dissolved in 10 ml water, cooled, basified with 6N-NaOH. The separated oil was extracted with $CHCl_3$, $CHCl_3$ extract washed with water, dried ($Na_2SO_4$) and solvent was removed to give **14**, yield 1.55 g (80 %), IR (Neat): 3040 (arom.), 1615 $cm^{-1}$ (C=N); PMR ($CCl_3$): δ (ppm) = 1.05–2.1 (m, 9, aliphatic H), 2.3–2.9 (m, 6, $-NCH_2$), 3.37 (s, 2H, Ar-$C\underline{H}_2$-N), 3.78 (s, 6, $-OCH_3$), 6.55 (s, 1, Ar-$\underline{H}$-5′), 6.82 (s, 1, Ar-$\underline{H}$-8′), 7.13 (s, 5, Ar-$\underline{H}$).

Similarly **15** was prepared from **13**, yield (76 %), IR (Neat): 2860 ($CH_2$), 1622 $cm^{-1}$ (C=N); PMR ($CDCl_3$): δ (ppm) = 1.05–2.10 (m, 7, -$C\underline{H}$, -$C\underline{H}_2$), 2.13 (s, 3, $-NCH_3$), 2.3–3.05 (m, 6, $-NCH_2$), 3.55 (d, 2, Ar-$C\underline{H}_2$-), 3.8 (s, 6, $-OCH_3$), 6.55 (s, 1H, Ar-H-5′), 6.83 (s, 1, Ar-H-8′).

*1-Benzyl-4-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolylmethyl)piperidine* **(16)**

2.1 g sodium borohydride was added in portions to a stirred solution of 5.04 g (0.0133 mol) **14** in 100 ml methanol at 0°C and the stirring was continued at 30°C for another 4 h. The reaction mixture was concentrated i. vac., the residue taken in water, extracted with $CHCl_3$, organic layer was washed with water, dried ($Na_2SO_4$) and solvent was removed to give **16** as a thick oil, yield 3.8 g (76 %). The dihydrobromide salt was prepared and crystallised from MeOH-ether, m.p. 135–140°C, IR (Neat): 3500 $cm^{-1}$ (NH); PMR ($CDCl_3$): free base δ (ppm) = 1.27–2.18 (m, 9, -$C\underline{H}$, -$C\underline{H}_2$), 2.42–3.2 (m, 7, -$C\underline{H}$, -$NC\underline{H}_2$), 2.4 (s, 2, Ar-$C\underline{H}_2$-N), 3.73 (s, 6, $OCH_3$), 6.14 (s, 2, Ar-$\underline{H}$-5′, and H-8′), 7.14 (s, 5, Ar-$\underline{H}$).

Similarly the compound **17** was prepared from **15.** Dihydrobromide of **17** was prepared and crystallized from MeOH-ether. **17**, yield 87 %, m.p. 182–185°C. IR (KBr) as **17.** 2 · HBr: 3500 (NH), 2950 $cm^{-1}$ (arom.); PMR ($CDCl_3$): δ (ppm) = 1.37–2.05 (m, 9, $C\underline{H}$, $C\underline{H}_2$, Ar-$C\underline{H}_2$), 2.19 (s, 3, $NCH_3$), 2.5–3.2 (m, 7, $NCH_2$, $NC\underline{H}$), 3.7 (s, 6, $OCH_3$), 4.2 (bs, 1, NH), 6.43 (s, 2, Ar-H-5′ and H-8′).

*1-Benzyl-4-(2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolylmethyl)piperidine* **(20)**

0.126 g (1,6 mmol) acetylchloride was added dropwise to a well stirred solution of 0.57 g (1,5 mmol) **16** and 0.166 ml (1,65 mmol) triethylamine in 15 ml dry benzene at 0°C. The reaction mixture was stirred for additional 10 h. The separated salt was filtered and filtrate was successively washed with saturated $NaHCO_3$ solution and water, the benzene layer was dried ($Na_2SO_4$), concentrated and triturated with ether to give **20** as crystalline solid, yield 0.35 g (55 %), m.p. 117–120°C, IR (KBr): 2920 (arom.), 1640 $cm^{-1}$ (NCO); PMR ($CDCl_3$): δ (ppm) = 1.1–2.0 (m, 9, $C\underline{H}_2$, $C\underline{H}$), 2.07 (s, 3, $-COCH_3$), 2.45–3.1 (m, 6, $-NCH_2$), 3.4 (s, 2, $-NCH_2$), 3.73 (s, 6, $OCH_3$), 4.35–4.75 (m, 0.5, N-CH), 5.45–5.72 (dd, 0.5, N-CH), 6.4 (bs, 2, Ar-H-5′ and H-8′), 7.13 (bs, 5, Ar-$\underline{H}$).

Similarly **21** and **22** were prepared from **16** and **17** and the corresponding acid chloride. **21** yield 41 %, m.p. 227–230°C. IR (KBr): 2930 (arom.), 2800 ($CH_2$), 1630 $cm^{-1}$ (NCO); PMR ($CDCl_3$): δ (ppm) = 1.15–3.5 (m, 17, -$C\underline{H}$, -$NC\underline{H}_2$), 3.76 (s, 6, $-OCH_3$), 4.4–4.9 (m, 0.5H, NCH), 6.45 (bs, 2, Ar-H-5′ and H-8′), 7.07–7.4 (m, 10, Ar-$\underline{H}$). **22**, yield 46 %, m.p. 115–117°C. IR (KBr): 1640 $cm^{-1}$ (NCO); PMR ($CDCl_3$): δ (ppm) = 1.15–2.0 (m, 7, -$C\underline{H}$, -$C\underline{H}_2$), 2.10 (s, 3, $-NCH_3$), 2.17 (s, 3, $-COCH_3$), 2.45–3.60 (m, 8, N-$C\underline{H}_2$, Ar-$C\underline{H}_2$), 3.75 (s, 6, $-OCH_3$), 4.3–4.75 (m, 0.5, NCH), 5.4–5.7 (dd, 0.5H, NCH), 6.41 (bs, 2, Ar-H-5′ and H-8′).

*1-Benzyl-4-[β-(3,4-dimethoxyphenyl)ethyl]aminoethylpiperidine* **(19)**

A suspension of 0.15 g $LiAlH_4$ and 0.396 g (1 mmol) **12** in 20 ml dry THF was refluxed for 10 h, the complex was decomposed by successive addition of water, 2.5 N-NaOH and water. The complex was filtered and the filtrate was evaporated to give **18** as a thick oil, yield 0.25 g (65 %); IR (Neat): 3350

$cm^{-1}$ (NH); PMR ($CDCl_3$): δ (ppm) = 1.1–2.05 (m, 9, C<u>H</u>, C<u>$H_2$</u>), 2.4–2.95 (m, 6, –N<u>$CH_2$</u>), 3.25–3.6 (m, 4, –N<u>$CH_2$</u>, –N<u>$CH_2$</u>–Ar), 3.76 (s, 6, $OCH_3$), 4.4–4.5 (m, 1, –N<u>H</u>), 6.5–6.8 (m, 3, Ar–H-5′, H-8 and H-8′a), 7.12 (s, 5, Ar–<u>H</u>).

Similarly **19** was prepared from **13** as an oil, yield 69 %. IR (Neat): 3400 (NH), 2940 $cm^{-1}$ (arom.); PMR ($CDCl_3$): δ (ppm) = 1.0–2.0 (m, 9, –C<u>H</u>, –C<u>$H_2$</u>, Ar–C<u>$H_2$</u>), 2.14 (s, 3, –$NCH_3$), 2.3–3.6 (m, 8, –N<u>$CH_2$</u>), 3.75 (s, 6, $OCH_3$), 4.5 (bs, 1H, N<u>H</u>), 6.5–6.75 (m, 3, Ar–H-5′, H-8′ and H-8′a).

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# Aminomethylierung von Enaminoestern

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3-Amino- und 3-Methylaminocrotonsäureethylester ergeben mit Formaldehyd und sekundären Aminen C-Aminomethylprodukte der Enamin-Struktur, wobei in Lösung ausschließlich bzw. hauptsächlich die *Z*-Formen vorliegen. 3-Dimethylaminocrotonsäureethylester ist keiner entsprechenden Umsetzung zugänglich, reagiert jedoch als vinyloge Carbonylverbindung mit Dimethylmethyleniminiumchlorid unter Aminomethylierung der Allyl-Methylgruppe.

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[x] Herrn Professor Dr. Dr.h.c. *Kuno Meyer* mit den besten Wünschen zum 70. Geburtstag gewidmet.

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