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A HIGHLY STEREOSELECTIVE SYNTHESIS OF 3,4-DIHYDRO-1(2*H*)-ISOQUINOLINONES AND 8-OXOBERBINES FROM HOMOPHTHALIC ANHYDRIDES AND AZOMETHINES[1]

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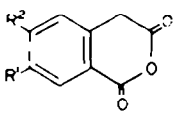
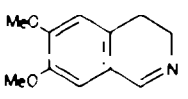
Abstract—The interaction between 1,3-isochromanediones(homophthalic anhydrides) **1** and acyclic azomethines of types **2** and **3** and the cyclic 6,7-dimethoxy-3,4-dihydroisoquinoline **4** is investigated. The former lead in high yields to the (±)-trans-3-aryl-4-carboxy-3,4-dihydro-1(2*H*)-isoquinolinones **5**, while the latter gives the (±)-cis-13-carboxy-8-oxoberbines **7**. The relative configurations of compounds **5–8** as well as the preferred conformations of some compounds of type **5** and of all of type **6** are determined by chemical correlation and NMR.

Schiff bases are easily acylated with acyl halides or anhydrides,[2] and the resulting adducts may be used in the synthesis of heterocyclic compounds.[3,4] In the present work we wish to describe the results from our studies on the interaction of 1,3-isochromanediones(homophthalic anhydrides) **1a–c** with azomethine compounds of types **2**, **3** and **4**. The reaction of homophthalic anhydrides with Schiff bases of "hydroamides" of aromatic aldehydes (**2** or **3**, respectively) is a new approach leading to (±) - trans - 3 - aryl - 4 - carboxy - 3,4 - dihydro - 1(2*H*) - isoquinolinones(trans - **5**) in one step. The reaction proceeds at room temperature or gentle reflux in rather concentrated benzene or dichloroethane solutions the products almost immediately crystallizing on dissolution. In this manner were obtained compounds trans-**5a—k** in 70% to quantitative yields.[18] From compounds trans-**5a–k** were prepared via diazomethane treatment the corresponding methyl esters trans-**6a–k**.

The 1,3 - isochromanediones **1a** and **1b** react with 6,7 - dimethoxy - 3,4 - dihydroisoquinoline **4** in dilute



1a–c
a: R¹ = R² = H
b: R¹ = R² = MeO
c: R¹ + R² = CH_2O_2



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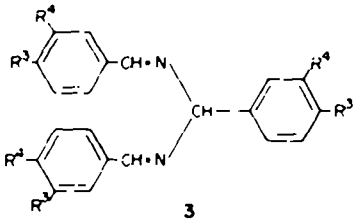

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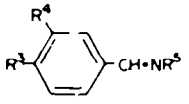

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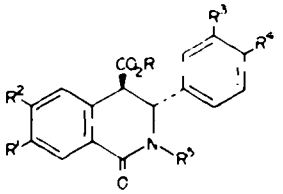


trans - **5a–k**: R = H
trans - **6a–k**: R = Me

	R^1	R^2	R^3	R^4	R^5
a	H	H	H	H	Me
b	CH_3O	CH_3O	H	H	Me
c	CH_2O_2		H	H	Me
d	CH_3O	CH_3O	CH_2O_2		Me
e	H	H	CH_3O	CH_3O	Me
f	H	H	H	H	Ph
g	H	H	H	H	Et
h	H	H	H	H	n-Pr
i	H	H	H	H	iso-Pr
j	H	H	H	H	H
k	H	H	CH_2O_2		H

dichloroethane solution in the presence of triethylamine to give in good yields the 13 - carboxy - 8 - oxoberbines cis-**7a** and cis-**7b** isolated and identified as the respective 13 - methoxycarbonyl - 5,6,13,14 - tetrahydro - 8*H* - dibenzo[a,g]quinolizine - 8 - ones cis-**8a** and cis-**8b**. 13 - Carboxy - didehydro - 8 - oxoberbine **10**, characterized as 13 - methoxycarbonyl - didehydro - 8 - oxoberbine **11**, was also isolated, its structure being established on the basis of IR and NMR spectra which closely resembled those of compounds with similar structure.[6]

Reduction of **8a** with lithium aluminum hydride affords (±) - cis - 2,3 - dimethoxy - 13 - hydroxymethyl - 5,6,13,14 - tetrahydro - 8*H* - dibenzo[a,g]quinolizine, cis-**9a**. The outlined procedure for synthesizing berbine structures containing a carbon moiety at C-13 can be employed in the preparation of protoberberine alkaloids of the corydaline and cavidine types.[7]

Attempts to use 2 - methyl - 1,3(2*H*,4*H*) - isoquinolinedione **12** as starting compound containing acidic hydrogen atoms showed it to be insufficiently reactive. With benzylidenemethylamine in the presence or absence of triethylamine it gave complex reaction mixtures containing about 50% starting material.

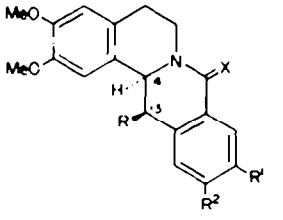
Relative configurations and preferred conformations of the isoquinoline derivatives

The relative configurations of the 4 - carboxy - dihydroisoquinolinones **5** were established by chemical correlation with their respective methyl esters **6**. The trans-configuration of the 4 - methoxycarbonyl - dihydroisoquinilinones **6** was determined by direct comparison with authentic samples as well as by comparing their NMR spectra.

The diastereomeric dihydroisoquinolinones of type **6** were obtained without configurational changes via the oxidation of trans- and cis-tetrahydroisoquinolines of type **13** with potassium permanganate in acetone.[8,9] It was found that the protons of the methoxycarbonyl groups in both types of compounds, i.e. **13**[10] and **6**,[8,9] resonate in the trans-isomers at lower fields than for the cis isomers, probably because of greater screening effect of the phenyl groups in the latter (trans-**13** δ: 3.45–3.66; trans-**6** δ: 3.68–3.78; cis-**13** δ: 3.32–3.39; cis-**6** δ: 3.37–3.48).

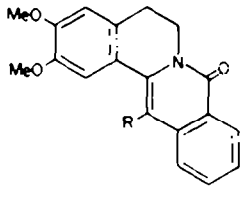
All newly prepared compounds **6** have NMR spectra closely resembling the ones of the previously described trans-isomers. Compounds trans-**5a,b,c** were found to be identical with previously synthesized samples of the same compounds. It is worth mentioning that the ester trans-**6d** was prepared by us in a crystalline modification (m.p. 181–182°) different from the reported one (m.p. 194–195°).[8] Both products had different melting points, but identical elemental analyses, IR and NMR spectra. On seeding the solution of the sample melting at 181–182° with crystals melting at 194–195° were obtained crystals that melted at 198–199°, very likely of higher stereochemical purity. The melting point of a mixture of the latter with the ones melting at 194–195° remained undepressed.

The preferred conformations of all compounds of type **6** and of some compounds of type **5** were established from their NMR spectra. Compounds trans-**5** and trans-**6** with N-methyl, N-alkyl or N-phenyl groups exhibit, similarly to the previously prepared samples with N-methyl groups,

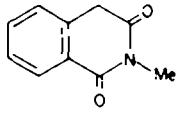


cis - **7a, b**: R = CO_2H, X = O
cis - **8a, b**: R = CO_2Me, X = O
cis - **9a** : R = CH_2OH, X = 2H

	R¹	R²
a	H	H
b	MeO	MeO



10: R = CO_2H
11: R = CO_2Me



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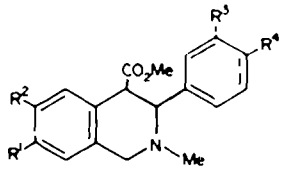
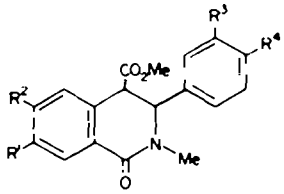


trans - and *cis* - **13a-c**



trans - and *cis* - **6a-c**

	R¹	R²	R³	R⁴
a	MeO	MeO	H	H
b	CH_2O_2		H	H
c	MeO	MeO	CH_2O_2	

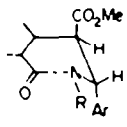
low vicinal spin-spin coupling constants ($J_{3,4}$ = 1–1.5 Hz). The compounds with unsubstituted nitrogen, i.e. trans-**5** and **6** possess high spin-spin coupling constants ($J_{3,4}$ = 6.5–6.8 Hz for trans-**6**). The tendency towards planarity arising from the conjugation between the amide function and the phenyl group renders the conformers with C-3 carbon atoms out of the average plane of the ring most probable (**14** and **15**). The low $J_{3,4}$ values observed for the N-substituted compounds are in agreement with conformation **14**. The pseudo-axial orientation of the substituents at C-3 and C-4 is more favourable because of the diminished repulsive interactions between the nitrogen substituent and the aryl group. The $J_{3,4}$ constants for the unsubstituted at the nitrogen representatives support conformation **15** with pseudo-equatorial substituents at C-3 and C-4.

A new reaction between homophthalic anhydride and the Vilsmeier reagent leading to N-methyl-1(2*H*)-isoquinolones in good yields was described[16] shortly after our preliminary communication[1] was sent to the publishers. As the authors point out, homophthalic anhydride formed under the reaction conditions actually takes part in the process.

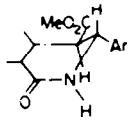
Our studies on ring-forming reactions between various isochromanedione-related CH acidic compounds and azomethines of different structures are continuing.

EXPERIMENTAL

The m.ps were taken on a Kofler hot-stage and are uncorrected. TLC was carried out on silica gel according to Stahl(Merck). The solvent systems used were: ether/hexane (1:1) (system A), ether/hexane (2:1) (system B), ether/benzene (2:1) (system C),



14: R = Me, Alkyl, Ph



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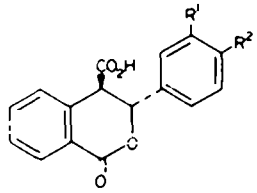

trans-**16a, b**

	R¹	R²
a	CH_2O_2	
b	H	H

The NMR spectra of the compounds cis-**8a** and cis-**8b** indicate that the protons at C-13 and C-14 are of cis configuration ($J_{13,14}$ = 4.5 Hz for cis-**8a** and 4.5 Hz for cis-**8b**) a conclusion corroborated also by data of other authors[11] regarding the stereochemistry of tetrahydroprotoberberine alcaloids with a methyl group at C-13. The IR spectrum of the dibenzoquinolizidine cis-**9a** exhibits clearly observable Bohlmann absorption bands in the 2840–2600 cm^{-1} region and is devoid of absorption due to free hydroxyl groups. These Bohlmann bands correspond by position and intensity well to the ones seen in the IR spectra of similar compounds, for example the alkaloid lupinine.[11] It can be concluded on the basis of these data that compound cis-**9a** has the protons at C-13 and C-14 in cis-configuration, while the ring fusion is of the trans-quinolizidine type.[11]

The reaction between homophthalic anhydrides and azomethines proceeds stereoselectively yielding mainly or solely one of the possible diasteromeric products. It is worth noting that the interaction between homophthalic anhydride **1a** and aromatic aldehydes in the presence of basic catalysts giving 3 - aryl - 4 - carboxy - 3,4 - dihydroisocoumarins[13] also proceeds stereoselectively. Thus, the dihydroisocoumarins trans-**16a** and **b** obtained from **1a** and piperonal[14] or benzaldehyde[9] are of trans configuration (on the basis of their NMR spectra). The reaction leading to β-lactams[4] from acid chlorides and imines in the presence of a base, however, runs to either the trans product only or to a mixture of cis and trans β-lactams. Stereoselective preparations of β-lactams by the described above procedure have been reported only in a few cases.[15] The high stereoselectivity observed in the present investigations can be taken as an indication of a concerted mechanistic pathway. Studies aiming at obtaining additional information regarding the mechanism of the reaction are currently under way.

hexane/ethyl acetate/methanol/ammonia (12:10:1.5:1), top layer (system D). The IR spectra were measured on UR 10 (Zeiss) and Specord 71 IR (Zeiss) spectrometers using 1% $CHCl_3$ solutions or Nujol. The NMR spectra were recorded on Jeol JNM-C-60-S, "Tesla" BS-487-C (80 MHz) or Jeol JNM-PS-100 spectrometers in $CDCl_3$ with TMS as internal standard.

(±) - *trans* - 3 - *Aryl* - 4 - *carboxy* (*and* 4 - *methoxycarbonyl*) - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans*-**5** *and trans*-**6**. *General procedure*. To 1 mmole of 1,3 - isochromanedione (homophthalic anhydride) **1** and 1 mmole of azomethine **2**, or 0.5 mmole of **3**, 2 ml of dichloroethane were added. The mixture was refluxed for 10 min to achieve homogeneity and the resulting solution was allowed to stand at room temp. for 1 h. In some cases the 4 - carboxy - dihydroisoquinolinone **5** precipitated immediately and the solid product was filtered off. In all cases the dichloroethane solution was extracted with 10% sodium hydroxide (3 × 3 ml). The alkaline solution was acidified with 1:1 hydrochloric acid to give the solid 4-carboxyisoquinolinone **5**. This material was purified by crystallization if crystalline, if amorphous—by dissolving in 5% aq K_2CO_3 repeated precipitation with hydrochloric acid. The dichloroethane solution was evaporated to dryness *in vacuo* and the small residue was not examined further.

A solution of 0.5 mmoles of **5** in dimethylform-amide (DMFA) or dimethylsulphoxide (DMSO) 1-2 ml and diluted with 5 ml of dichloroethane was treated with ethereal diazomethane solution. The reaction mixture was worked up the next day in the usual manner yielding the crude ester quantitatively.

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 2 - *methyl* - 3 - *phenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans*-**5a** *and trans*-**6a**). From 1,3 - isochromanedione **1a** (162 mg) and benzylidene methylamine (**2**: R¹ = R⁴ = H, R³ = CH_3) (120 mg) was obtained crude trans-**5a** with m.p. 202–203°, 256 mg (91%), on recrystallization from ethanol–water m.p. 205–206°. Found: C, 72.42; H, 5.38. Calc. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37%. IR (Nujol) cm^{-1}: 1635 (CO amide), 1710, 2400–3200 and 3530 (CO_2H). NMR (80 MHz) δ: 5.25 (1H, d, $J_{3,4}$ = 1 Hz, C-3H), 3.92 (1H, d, C-4H), 3.10 (3H, s, NCH_3), 9.0 (1H, CO_2H), 6.9–7.6 (8 arom H, m), 8.1 (1H, m, C-8H).

From trans-**5a** (141 mg) m.p. 202–203° in DMSO was obtained

trans-**6a**, single spot by TLC (system B). On recrystallization from ether m.p. 106–107°, 79 mg (67%). The analytically pure substance had m.p. 107–108°. Found: C, 73.40; H, 6.01. Calc. for $C_{18}H_{17}O_3N$: C, 73.20; H, 5.80%. IR ($CHCl_3$) cm $^{-1}$: 1650 (CO amide), 1735 (CO ester). NMR (60 MHz) δ: 5.35 (1H, d, $J_{3,4}$ = 1.3 Hz), 4.0 (1H, d, C-4H), 3.20 (3H, s, NCH_3), 3.75 (3H, s, CO_2CH_3), 7.0–7.6 (8 arom, H, m), 8.3 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 6,7 - *dimethoxy* - 3 - *phenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans*-**5b** *and trans*-**6b**). From a mixture of 6,7 - dimethoxy - 1,3 - isochromanedione **1b** (222 mg) and benzylidene methylamine (120 mg) were obtained in crystalline form 94 mg of trans-**5b**, m.p. 214–216°. Extraction with aq NaOH and further purification in the usual manner afforded a second portion of amorphous trans-**5b** (192 mg). The total yield reached in this way 83%. After a twofold recrystallization from ethanol, m.p. 225–226°. Found: C, 67.04; H, 5.75. Calc. for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61%. IR (Nujol) cm $^{-1}$: 1620 (CO amide), 1740, 2400–3200 (CO_2H).

From amorphous trans-**5b** (171 mg) in DMSO was obtained oily trans-**6b**, single spot by TLC (system C). Recrystallization from benzene–hexane afforded 158 mg (78%) of trans-**6b**, m.p. 155–156° which did not change on further recrystallization. Found: 67.66; H, 6.20. Calc. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96%. IR ($CHCl_3$) cm $^{-1}$: 1650 (CO amide), 1735 (CO ester). NMR (80 MHz) δ: 5.18 (1H, d, $J_{3,4}$ = 1.5 Hz, C-4H), 3.80 (1H, d, C-3H), 3.12 (3H, s, NCH_3), 3.68 (3H, s, CO_2CH_3), 3.80 and 3.92 (2 × 3H, each s, $2CH_3O$), 6.60 and 7.68 (2 × 1H, each s, C-5H and C-8H), 7.0–7.4 (5 arom, H, m). This material was shown to be identical by m.p., IR, and NMR spectra with a sample of the same compound described in Ref. 8.

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 6,7 - *methylenedioxy* - 2 - *methyl* - 3 - *phenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5c** *and trans* - **6c**). From 6,7 - methylenedioxy - 1,3 - isochromanedione **1c** (206 mg) and benzylidene methylamine (120 mg) via extraction with aq NaOH and the usual purification procedure was obtained amorphous trans-**5c**, 282 mg (92%).

From trans-**5c** was obtained in DMSO trans-**6c**, a single spot by TLC (system B). Recrystallization from benzene–hexane afforded trans-**6c** in 78% yield, m.p. 151-152°. This material was found to be identical by mixed m.p., TLC (system B) and IR spectrum with a sample of the same compound as described in Ref. 8. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1730 (CO ester).

To trans-**6c** (100 mg) dissolved in ethanol (5 ml) was added a 10% aq KOH (5 ml) and the resulting mixture was heated at 90° for 1 h. The ethanol was then removed and the residue diluted with water. Precipitation with HCl gave 90 mg (97%) of trans-**5c**, m.p. 225–227°, after recrystallization from ethanol m.p. 228–229°. Found: C, 66.56; H, 4.85. Calc. for $C_{18}H_{15}O_5N$: C, 66.45; H, 4.65%. IR (Nujol) cm $^{-1}$: 1645 (CO amide), 1705, 2400–3200 (CO_2H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 6,7 - *dimethoxy* - 2 - *methyl* - 3 - (3',4' - *methylenedioxyphenyl*) - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5d** *and trans* - **6d**). From the mixture of **1b** (222 mg) and piperolidene methylamine (2, $R^1 + R^4 = CH_2O_2$, $R^3 = CH_3$) (131 mg) was obtained in crystalline form trans-**5d** (210 mg), m.p. 225–226°. Extraction with aq NaOH and further purification afforded a second fraction of crystals (150 mg), m.p. 224–226°, the total yield of trans-**5d** thus reaching 96%. The m.p. after recrystallization from ethanol 228–229°. Found: C, 59.26; H, 5.36; N, 3.38. Calc. for $C_{20}H_{19}O_7N \cdot H_2O$: C, 59.55; H, 5.25; N, 3.47%. IR (Nujol) cm $^{-1}$: 1620 (CO amide), 1735, 2400–3200 (CO_2H).

From trans-**5d** (177 mg), m.p. 225–226° dissolved in DMSO was obtained trans-**6d** (oily form), a single spot by TLC (system D). On crystallization from benzene–hexane it gave trans-**6d** 158 mg (89%), m.p. 180–181°, after repeated recrystallization from methanol, m.p. 181–182°. Found: C, 62.90; H, 5.58. Calc. for $C_{21}H_{21}O_7N$: C, 63.15; H, 5.30%. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1730 (CO ester). NMR (80 MHz) δ: 5.10 (1H, d, $J_{3,4}$ = 1.5 Hz, C-3H), 3.78 (1H, d, C-4H), 3.10 (3H, s, NCH_3), 3.68 (3H, s, CO_2CH_3), 3.85 and 3.95 (2 × 3H, each s, $2CH_3O$), 5.88 (2H, s, CH_2O_2), 6.5–6.7 (3 arom, H, m), 6.62 (1H, s, C-5H), 7.65 (1H, s, C-8H).

Trans-**6d**, m.p. 180–181° was prepared in good yield from trans-**5d**, m.p. 224–226°. Recrystallization from methanol via seeding the solution with trans - 6,7 - dimethoxy - 4 - methoxycarbonyl - 2 - methyl - 3 - (3',4' - methylenedioxyphenyl) - 3,4 - dihydro - 1(2*H*) - isoquinolinone, m.p. 194–195° (Ref. 8) yielded a product m.p. 198–199°. Both samples were found to be identical by mixed m.p., TLC (system D) and IR spectra.

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 3 - (3',4' - *dimethoxyphenyl*) - 2 - *methyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5e** *and trans* - **6e**). From **1a** (162 mg) and veratrylidene methylamine (2, $R^1 = R^4 = CH_3O$, $R^3 = CH_3$) (178 mg) was prepared trans-**5e** (172 mg), m.p. 187–188°. Extraction with sodium hydroxide solution and further purification gave a second fraction of crystals of trans-**5e** (155 mg), m.p. 187–188° the total yield thus reaching 96%. After recrystallization from ethanol m.p. 193–194°. Found: C, 66.63; H, 5.95. Calc. for $C_{19}H_{19}O_4N$: C, 66.85; H, 5.61%. IR (Nujol) cm $^{-1}$: 1625 (CO amide), 1740, 2400–3200 (CO_2H).

From trans-**5e**, m.p. 187–188° (170 mg) dissolved in DMFA was obtained trans-**6e**, a single spot by TLC (system C). It was recrystallized from ether to give 150 mg (86%) of trans-**6e**, m.p. 110–111°, on repeated recrystallizations m.p. 111–112°. Found: C, 67.25; H, 6.16. Calc. for $C_{20}H_{21}O_5N$: C, 67.59; H, 5.96%. IR spectrum ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1735 (CO ester). NMR (80 MHz) δ: 5.18 (1H, d, $J_{3,4}$ = 1.5 Hz, C-3H), 3.90 (1H, d, C-4H), 3.12 (3H, s, NCH_3), 3.68 (3H, s, CO_2CH_3), 3.68 and 3.75 (2 × 3H, each s, $2CH_3O$), 6.5–7.5 (6 arom, H, m), 8.2 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 2,3 - *diphenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5f** *and trans* - **6f**). From **1a** (162 mg) and benzylidene aniline (181 mg) and extraction with aq NaOH gave trans-**5f**, 225 mg (65%), m.p. 202–203°, on recrystallization from methanol m.p., 203–204°. Found: C, 76.66; H, 5.12. Calc. for $C_{29}H_{23}O_3N$: C, 76.95; H, 4.99%. IR (Nujol) cm $^{-1}$: 1635 (CO amide), 1730, 2400–3200 (CO_2H). NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ: 5.56 (1H, d, $J_{3,4}$ = 1 Hz, C-3H), 4.04 (1H, C-4H), 7.0–7.4 (13 arom, H, m), 7.9 (1H, m, C-8H).

From trans-**5e** (171 mg), m.p. 202–203° dissolved in DMFA was obtained trans-**6f** as an oil, a single spot by TLC (system A). It was recrystallized from benzene–hexane to give 116 mg (65%) of trans-**6f**, m.p. 161–162°, on repeated recrystallization from methanol m.p. 162–163°. Found: C, 77.63; H, 5.61. Calc. for $C_{21}H_{19}O_3N$: C, 77.29; H, 5.36%. IR ($CHCl_3$) cm $^{-1}$: 1655 (CO amide), 1735 (CO ester). NMR (60 MHz) δ: 5.72 (1H, d, $J_{3,4}$ = 1.5 Hz, C-3H), 4.08 (1H, d, C-4H), 3.78 (3H, s, CO_2CH_3), 7.2–7.7 (13 arom, H, m), 8.3 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 2 - *ethyl* - 3 - *phenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5g** *and trans* - **6g**). From **1a** (162 mg) and benzylidene ethylamine (133 mg) via extraction with sodium hydroxide solution was obtained trans-**5g**, 257 mg (87%), m.p. 204–206°, on recrystallization from ethanol m.p. 205–206°. Found: C, 69.30; H, 5.84; N, 4.44. Calc. for $C_{19}H_{19}O_4N \cdot H_2O$: C, 68.99; H, 6.11; N, 4.47%. IR (Nujol) cm $^{-1}$: 1630 (CO amide), 1730, 2400–3200 (CO_2H).

From trans-**5g** (150 mg) m.p. 204–206° dissolved in DMFA was prepared trans-**6g**, an oil, a single spot by TLC (system B : D = 1 : 1). On recrystallization from benzene–hexane were obtained crystals 135 mg (90%), m.p. 102–103°, after repeated recrystallization from methanol m.p. 103–104°. Found: C, 74.00; H, 6.26. Calc. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19%. IR ($CHCl_3$) cm $^{-1}$: 1635 (CO amide), 1725 (CO ester). NMR (80 MHz) δ: 5.21 (1H, d, $J_{3,4}$ = 1.25 Hz, C-3H), 3.82 (1H, d, C-4H), 2.86 and 4.08 (2 × 1H, each m, NCH_2CH_3), 1.12 (3H, t, NCH_2CH_3), 3.60 (3H, s, CO_2CH_3), 6.8–7.5 (8 arom, H, m), 8.1 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 3 - *phenyl* - 2 - *n* - *propyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5h** *and trans* - **6h**). From **1a** (162 mg) and benzylidene n-propylamine (147 mg) via extraction with sodium hydroxide solution was prepared trans-**5h**, 306 mg (99%), m.p. 166–168°, on recrystallization from ethanol m.p. 167–168°. Found: C, 73.83; H, 6.11. Calc. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19%. IR (Nujol) cm $^{-1}$: 1630 (CO amide), 1730, 2400–3200 (CO_2H).

From trans-**5h** (155 mg), m.p. 166–168° dissolved DMFA was prepared trans-**6h**, a single spot by TLC (system B). It was recrystallized from benzene–hexane to give 140 mg (93%) trans-**6h**, m.p. 163–164°, on repeated recrystallization from

methanol m.p. 164–165°. Found: C, 74.41; H, 6.79. Calc. for $C_{20}H_{21}O_3N$: C, 74.28; H, 6.55%. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1730 (CO ester). NMR (80 MHz) δ: 5.21 (1H, d, $J_{3,4}$ = 1 Hz, C-3H), 3.85 (1H, d, C-4H), 2.69 and 4.05 (2 × 1H, each m, $NCH_2CH_2CH_3$), 1.58 (2H, m, $NCH_2CH_2CH_3$), 0.82 (3H, t, $NCH_2CH_2CH_3$), 3.62 (3H, s, CO_2CH_3), 6.8–7.5 (8 arom. H, m), 8.1 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 3 - *phenyl* - 2 - *isopropyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5i** *and trans* - **6i**). From **1a** (162 mg) and benzylidene isopropylamine (147 mg) via extraction with sodium hydroxide solution was prepared 300 mg (97%) of trans-**5i** m.p. 180–181°, on recrystallization from ethanol m.p. 184–185°. Found: C, 73.80; H, 6.36. Calc. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19%. IR (Nujol) cm $^{-1}$: 1615 (CO amide), 1720, 2400–3200 (CO_2H).

From trans-**5i** (115 mg) m.p. 180–181° in DMFA solution was obtained trans-**6i**, a single spot by TLC (system B : D = 1 : 1), recrystallized from benzene–hexane to give 118 mg (77%) of trans-**6i**, m.p. 116–118° on repeated recrystallizations from methanol m.p. 118–119°. Found: C, 74.23; H, 6.80. Calc. for $C_{20}H_{21}O_3N$: C, 74.28; H, 6.55%. IR ($CHCl_3$) cm $^{-1}$: 1635 (CO amide), 1725 (CO ester). NMR (80 MHz) δ: 5.25 (1H, d, $J_{3,4}$ = 1.4 Hz, C-3H), 3.79 (1H, d, C-4H), 4.90 (1H, m, $NCH(CH_3)_2$), 0.82 and 1.16 (2 × 3H, each d, $NCH(CH_3)_2$), 3.62 (3H, s, CO_2CH_3), 6.8–7.5 (8 arom. H, m), 8.1 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 3 - *phenyl* - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5j** *and trans* - **6j**). From **1a** (162 mg) and hydrobenzamide (149 mg) was obtained and isolated via extraction with sodium hydroxide amorphous trans-**5j**. It was dissolved in aq K_2CO_3 and precipitated with hydrochloric acid to give 179 mg (67%) of trans-**5j**, m.p. 189–190° after two recrystallizations from aqueous ethanol. Found: C, 72.17; H, 5.29. Calc. for $C_{18}H_{15}O_3N$: C, 71.90; H, 4.90%. IR (Nujol) cm $^{-1}$: 1640 (CO amide), 3270 (NH amide), 1710 with inflexion at 1730 (CO_2H). NMR (80 MHz) δ: 5.35 (1H, m, C-3H), 4.00 (1H, d, $J_{3,4}$ = 3.5 Hz, C-4H), 7.0–7.6 (8 arom. H, m), 8.2 (1H, m, C-8H).

From the amorphous trans-**5j** (133 mg) in DMSO solution was obtained trans-**6j**, an oil, one main spot by TLC (system D). On recrystallization from benzene hexane 97 mg (62%) of material m.p. 152–154°, after recrystallization from methanol m.p. 156–157°. Found: C, 72.37; H, 5.58. Calc. for $C_{19}H_{17}O_3N$: C, 72.58; H, 5.37%. IR ($CHCl_3$) cm $^{-1}$: 1675 (CO amide), 3415 (NH amide), 1745 (CO ester). NMR (60 MHz) δ: 5.30 (1H, m, C-3H), 4.20 (1H, d, $J_{3,4}$ = 6.8 Hz, C-4H), 6.9 (1H, NH), 3.71 (3H, s, CO_2CH_3), 7.0–7.6 (8 arom. H, m), 8.2 (1H, m, C-8H).

(±) - *trans* - 4 - *Carboxy* (*and* 4 - *methoxycarbonyl*) - 3 - (3',4' - *methylenedioxyphenyl*) - 3,4 - *dihydro* - 1(2H) - *isoquinolinones* (*trans* - **5k** *and trans* - **6k**). From **1a** (162 mg) and "Hydroamide" from piperonal (3, R^3 + R^4 = CH_2O_2)[17] (215 mg) was obtained in crystalline form trans-**5k** 193 mg, m.p. 244–246°. Extraction with sodium hydroxide solution and further purification afforded a second fraction of this material, 92 mg, m.p. 242–244°, the total yield being thus 92%. An analytically pure sample was prepared by recrystallization from ethanol, m.p. 247–248°. Found: C, 65.35; H, 4.46. Calc. for $C_{19}H_{13}O_5N$: C, 65.59; H, 4.21%. IR (Nujol) cm $^{-1}$: 1630 (CO amide), 3260 (NH amide), 1705, 2400–3200 (CO_2H).

From trans-**5k** (155 mg), m.p. 244–246° dissolved in DMFA was obtained trans-**6k**, a single spot by TLC (system D). This material was recrystallized from benzene–hexane to give 128 mg (79%) of trans-**6k**, m.p. 196–197° (subl.). Recrystallization from methanol gave trans-**6k** m.p. 199–200° (subl.). Found: C, 66.70; H, 4.80. Calc. for $C_{18}H_{13}O_5N$: C, 66.45; H, 4.65%. IR ($CHCl_3$) cm $^{-1}$: 1675 (CO amide), 3430 (NH amide), 1740 (CO ester). NMR (80 MHz) δ: 5.15 (1H, m, C-3H), 4.10 (1H, d, $J_{3,4}$ = 6.5 Hz, C-4H), 3.68 (3H, s, CO_2CH_3), 5.92 (2H, s, CH_2O_2), 6.4–7.6 (6 aromatic H, m), 8.2 (1H, m, C-8H).

(±) - *cis* - 13 - *Methoxycarbonyl* - 2,3 - *dimethoxy* - 5,6,13,14 - *tetrahydro* - 8H - *dibenzo*[a,g]*quinolizine* - 8 - *one* (*cis*-**8a**). To a solution of **4** (382 mg, 2 mmoles) and triethylamine (0.28 ml, 2 mmoles) in 12 ml of dry dichloroethane was added at room temp dropwise with stirring over a period of 15 min **1a** (324 mg, 2 mmoles) dissolved in 6 ml of dry dichloroethane. The reaction mixture was stirred for 0.5 h longer and allowed to stand overnight. It was then extracted with aq NaOH and the alkaline extracts were acidified to give 640 mg solid. The latter was treated with ethereal diazomethane solution to obtain an oily residue which was passed through a Kieselgel 60 "Merck" column (45 g). Hexane–ethylacetate eluates (70 : 30) afforded two products. The first product was 2,3 - dimethoxy - 13 - methoxycarbonyl - 5,6 - dihydro - 8*H* - dibenzo[a,g]quinolizine - 8 - one (**11**) 40 mg, a single spot by TLC (system B : D – 2 : 1). After two recrystallizations from methanol m.p. 202–203°. Found C, 69.08; H, 5.29. Calc. for $C_{21}H_{19}O_5N$: 69.03; H, 5.24%. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1735 (CO ester). NMR (80 MHz) δ: 2.92 (2H, t-like, NCH_2CH_2), 4.25 (2H, t, J = 6 Hz, NCH_2CH_2), 3.75 (3H, s, CO_2CH_3), 3.82 and 3.90 (2 × 3H, each s, $2CH_3O$), 6.77 and 7.12 (2 × 1H, each s, C-1H and C-4H), 7.4–7.8 (3 arom. H, m), 8.4 (1H, m, C-9H). The second isolated product was cis-**8a**, a single spot by TLC (system B : D = 2 : 1). On recrystallization from benzene–hexane it gave 350 mg (48%) of cis-**8a**, m.p. 154–155°, after repeated recrystallization from methanol m.p. 157–158°. Found: C, 68.84; H, 5.56. Calc. for $C_{21}H_{21}O_5N$: C, 68.65; H, 5.67%. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1740 (CO ester). NMR (60 MHz) δ: 4.30 (1H, d, $J_{13,14}$ = 4.5 Hz, C-13H), 5.25 (1H, d, C-14H), 2.95 (2H, m, NCH_2CH_2), 3.40 (3H, s, CO_2CH_3), 3.94 and 3.96 (2 × 3H, each s, $2CH_3O$), 6.78 and 6.85 (2 × 1H, each s, C-1H and C-4H), 7.3–7.7 (3 arom. H, m), 8.3 (1H, m, C-9H).

(±) - *cis* - *Methoxycarbonyl* - 2,3,10,11 - *tetramethoxy* - 5,6,13,14 - *tetrahydro* - 8H - *dibenzo*[a,g]*quinolizine* - 8 - *one* (*cis*-**8b**). From **4** (382 mg), triethylamine (0.28 ml) and **1b** (444 mg) following the above described procedure were obtained 800 mg of a solid product (see preparation of cis-**8a**). It was converted into esters a part of which crystallized. This product was collected and recrystallized twice from methanol to yield 90 mg of cis-**8b**, m.p. 156–157°. A second fraction of cis-**8b** was obtained when the above mixture of esters was chromatographed over Kieselgel 60 "Merck" (45 g). Chloroform–ethylacetate eluates (80 : 20) afforded cis-**8b**, a single spot by TLC (system D). After two recrystallizations from methanol 310 mg of cis-**8b**, m.p. 156–157° were obtained. The total yield of cis-**8b** thus reached 47%. Found: C, 64.88; H, 6.16. Calc. for $C_{23}H_{25}O_7N$: C, 64.62; H, 5.90%. IR ($CHCl_3$) cm $^{-1}$: 1645 (CO amide), 1740 (CO ester). NMR (80 MHz) δ: 4.18 (1H, d, $J_{13,14}$ = 4.5 Hz, C-13H), 5.18 (1H, d, $J_{13,14}$ = 4.5 Hz, C-14H), 2.95 (2H, m, NCH_2CH_2), 3.45 and 4.0 (2 × 1H, m, NCH_2CH_2), 3.35 (3H, s, CO_2CH_3), 3.95 (12H, s, $4CH_3O$), 6.77 and 6.85 (2 × 1H, each s, C-1H and C-4H), 7.32 (1H, s, C-12H), 7.70 (1H, s, C-9H). (The m.p. of cis-**8a** and cis-**8b** were sometimes quite close, however, the m.p. of their mixture showed a depression.)

cis - *Dimethoxy* - 13 - *hydroxymethyl* - 5,6,13,14 - *tetrahydro* - 8H - *dibenzo*[a,g]*quinolizine* (*cis*-**9a**). A solution of cis-**8a** (367 mg, 1 mmole) dissolved in dry THF (27 ml) was reduced with $LiAlH_4$ (380 mg) by stirring and refluxing the mixture for 6 h. Excess hydride was destroyed with water and the solvent decanted. The solid material was extracted several times with benzene, the combined extracts were dried and the solvent removed to leave an uncrystallizable oil giving one main spot by TLC (system B). The substance was characterized as the hydrochloride salt, i.e. 261 mg (73%) m.p. 196–197° (from dry ethanol–dry ether). Found: C, 66.02; H, 6.82. Calc. for $C_{20}H_{24}O_3NCl$: C, 66.38; H, 6.70%.

From the above hydrochloride was obtained the free base. It was recrystallized twice from benzene–hexane and from methanol to give 173 mg (53%) of cis-**9a**, m.p. 152–153°. Found: C, 74.10; H, 7.33. Calc. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12%. IR (3×10^{-3} mole/l solution in CCl_4) cm $^{-1}$: broad band from 3120 to 3540 with a maximum at 3310 (bonded OH groups), no bands for free OH groups, 2765 and 2795 (Bohlmann bands).

REFERENCES

[1]Preliminary report presented at the *5th International Congress of Heterocyclic Chemistry*, Ljubljana, 13–18 July 1975.

[2]L. J. Heuser, C. F. Anderson, H. E. Applegate, E. H. Böhme, J. E. Dolfini and M. S. Puar, *J. Org. Chem.* **39**, 3929 (1974); and lit. cited.

[3]H. Böhme, S. Ebel and K. Hartke, *Chem. Ber.* **98**, 1463 (1965).

[4]A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya and M. S. Manhas, *Tetrahedron* **23**, 4769 (1967); A. K. Bose, G. Spiegelman and M. S. Manhas, *Tetrahedron Letters* 3167 (1971); A. K. Bose, Y. H. Chiang and M. S. Manhas, *Ibid.* 4091 (1972);

A. K. Bose, J. C. Kapur, S. D. Sharma and M. S. Manhas, *Ibid.* 2319 (1973).
[5]N. M. Mollov and A. P. Venkov, *Dokl. Bolg. Akad. Nauk* **28**(8), 1055 (1975).
[6]I. Ninomiya and T. Naito, *J.C.S. Chem. Comm.* 137 (1973); I. Ninomiya, T. Naito and H. Takasugi, *J.C.S. Perkin I* 1791 (1975).
[7]M. Shamma, *The Isoquinoline Alkaloids*, p. 269. Academic Press, New York (1972).
[8]M. A. Haimova, S. I. Novkova, S. L. Spassov and B. J. Kurtev, *Communications of the Department of Chemistry, Bulg. Acad. Sci.* **4**, 551 (1971).
[9]M. A. Haimova, to be published.
[10]M. A. Haimova, S. L. Spassov, S. I. Novkova, M. D. Palamareva and B. J. Kurtev, *Chem. Ber.* **104**, 2601 (1971).
[11]C. K. Yu, D. B. MacLean, R. G. A. Rodrigo and R. H. F. Manske, *Can. J. Chem.* **48**, 3673 (1970).
[12]J. Skolik, P. J. Krueger, M. Wiewiorowski, *Tetrahedron* **24**, 5439 (1968).
[13]E. Müller, *Ann.* **491**, 251 (1931); E. Müller, *Ibid.* **515**, 97 (1935).
[14]S. F. Dyke, M. Sainsbury and B. J. Moon, *J. Chem. Soc. C* 3935 (1971).
[15]A. K. Bose, B. Dayal, H. P. S. Chawla and M. S. Manhas, *Tetrahedron Letters* 2823 (1972); A. K. Bose, M. S. Manhas, H. P. S. Chawla and B. Dayal, *J. C. S. Perkin I* 1880 (1975).
[16]V. H. Belgaonkar and R. N. Usgaonkar, *Tetrahedron Letters* 3849 (1975).
[17]M. A. Haimova, M. D. Palamareva, S. I. Novkova, B. J. Kurtev, Z. A. Petrova and T. I. Arnaudov, *Mh. Chem.* **101**, 855 (1970).
[18]trans-**5k** is considered to be formed through hydrolysis of the initially-formed adduct of **1a** and **3** (R^3,R^4 = $-OCH_2-O$). No precautions were taken to avoid entry of water during the experiments.