Synthesis of *cis*- and *trans*-1,3-Dicarbomethoxy-2-aminoisoindoline (1)

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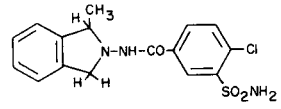
The title compounds (**4a,b**) were synthesized starting with dimethyl α,α'-dibromo-*o*-benzenediacetate and *t*-butyl carbazate. Alternate approaches to **4** involving reduction of the appropriate 2-nitrosoisoindoline were found unsuitable because of predominant side reactions.

J. Heterocyclic Chem., **18**, 475 (1981).

The recent discovery of high diuretic activity in 1-methyl-2-(4-chloro-3-sulfamoylbenzamido)isoindoline (**1**) (3) prompted us to investigate 1- or 1,3-disubstituted-2-aminoisoindolines, as precursors for potential diuretics related to **1**.



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The 1,3-dicarbomethoxy-2-aminoisoindoline (**4**) seemed worthy of synthesis for the following reasons: the potential easy transformation of the carbomethoxy substituent of **4** into a variety of other groups, and the *cis-trans* isomerism of **4**, which could allow the synthesis of two isomeric series of derivatives related to **1**, suitable for structure-activity studies.

This paper deals with the synthesis of the *cis*- and the *trans*-isomers of **4** by two methods, both starting from the known (4a) *meso*- (**2a**) and *d,l*-dimethyl α,α'-dibromo-*o*-benzene diacetate (**2b**).

It has been previously reported (4b) that the direct condensation of **2a,b** with the hydrazine hydrate gives 1,3-dicarbomethoxyisoindole (**5**) as the sole reaction product. We expected, however, that by replacing the latter reagent with *t*-butyl carbazate, 1,3-dicarbomethoxy-2-(*t*-butyloxycarbonylamino)isoindoline (**3**) might be obtained, which could give the desired **4** by acid cleavage of the protective group (5). Actually, both **2a** and **2b**, when reacted with *t*-butylcarbazate in dimethylformamide at 50° led to **3** as a mixture of the *cis* and the *trans* isomers, as determined by nmr. Besides these isomers, two other products were isolated in minor amount by column chromatography, which were identified as the known **5** (6), and as the dimethyl α-(*t*-butyloxycarbonylhydrazone)-*o*-benzenediacetate (**6**) (see Scheme 1). The nmr of **6** exhibited singlets at δ 1.48 (*t*-C_4H_9), 3.50 (-CH_2-) and 3.82 (2 CH_3OCO-), as well as a broad signal at δ 7.90 attributed to a =N-NH- group. To support the structure assigned, **6** was converted into 1-carbomethoxy-4,5-dihydro-3*H*-2,3-benzodiazepin-4-one (**8**) by stirring in a saturated solution of hydrogen chloride in ether.

Pure *cis*-**3a** and *trans*-**3b** were isolated by fractionated crystallization of the isomeric mixture from ether-petroleum ether. The stereochemistry of the two isomers was supported by the nmr shift of their methinic protons which, similar to other 1,3-dicarbomethoxyisoindolines (4a,7) lies at high field (δ 5.08) in the *cis* isomer, as compared with that (δ 5.40) of the *trans* isomer.

The remotion of the *t*-butyloxycarbonyl group from **3a,b** was accomplished in a saturated solution of hydrogen chloride in ether. While **3a** led to 52% of the expected *cis*-1,3-dicarbomethoxy-2-aminoisoindoline hydrochloride (**4a**), **3b** was converted into a mixture of *cis*-**4a** and *trans*-**4b** from which the latter was isolated in 30% yield by repeated crystallizations.

The reaction of **2a,b** with *t*-butyl carbazate deserves further comments. The formation of **3** as a mixture of *cis* and *trans* isomers seems consistent with a base-induced *meso* ⇌ *racemic* equilibration during the reaction (4b,7). Possible mechanisms for the formation of **5** and **6** are depicted in Scheme 2. While the isoindole **5** could derive from **3** by loss of *t*-butyl carbamate followed by a rearrangement of the thus formed isoindolenine (8), the isolation of **6** was somewhat unexpected. A reasonable hypothesis is suggested as the following. The open hydrazine intermediate (**12**) initially formed from **2** can loose hydrogen bromide intramolecularly, the proton being furnished by the acidic methine group, giving an *o*-quinoid structure (**13**) which rearranges to **6** by a nitrogen to carbon proton shift (9).

The unsatisfactory yields of **4b** from **2b** prompted us to consider alternative approaches to **4a,b**. As indicated in Scheme 1, *cis*-(**9a**) and *trans*-1,3-dicarbomethoxyisoindoline (**9b**) (4a) were easily transformed with nitrous acid into the corresponding *N*-nitroso derivatives *cis*-**10a** and *trans*-**10b**. Attempts to reduce the nitroso group of **10a,b** to amino group with hydrogen and palladium failed, both isomers being converted into **9a** and **5**. Cleavage of the N-N bond was avoided by reducing **10a,b** with zinc in acetic acid, but in this case **4a** along with **5** were the products isolated. Suspecting that the failure in isolating **4b** from **10b** was due to a *trans* ⇌ *cis* isomerization induced by the base employed in working up the acid reaction mixture, we attempted to isolate both **4a** and **4b** as the benzylidene derivatives **11a,b**. Actually, the latter compounds could be easily separated by adding benzaldehyde to the final acetic acid solutions. However, attempted acid

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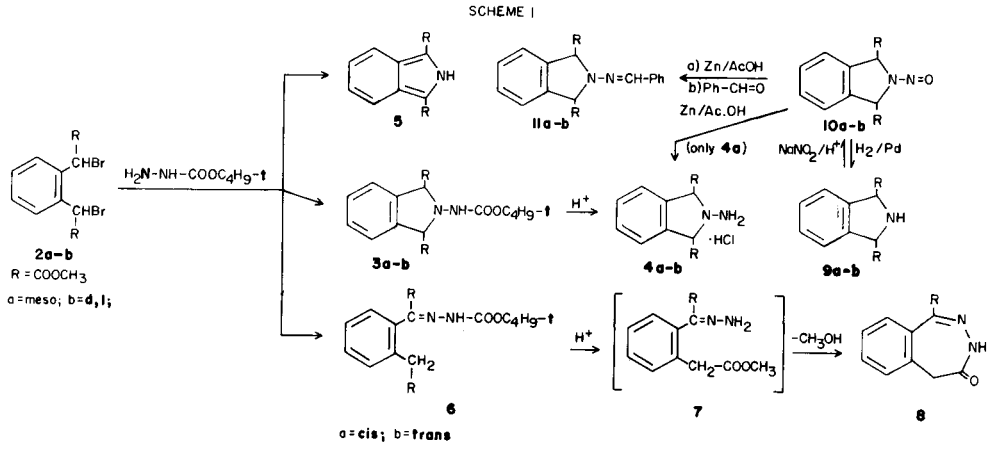
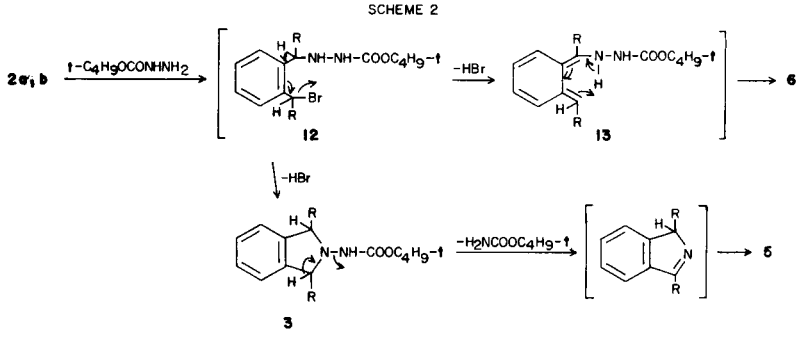
SCHEME 1



SCHEME 2



cleavage of the benzal group of **11** under mild conditions was not successful.

It is to note that the above reported evidences of *trans* → *cis* isomerization of isoindolines are in agreement with the known greater stability of the *cis* configuration in 1,3-isoindolinedicarboxylic acid derivatives (7). Also the observed formation of **5** still under reducing conditions is not surprising when the facile aromatization of 1,3-dicarbomethoxyisoindolines to the corresponding isoindoles, and the stability toward various reducing agents of the pyrrole moiety of the latter compounds (6) were taken into account.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the University of Padua. Ir spectra were recorded on a Perkin-Elmer 297 spectrophotometer and nmr spectra using a Perkin-Elmer R-24 spectrometer (TMS as internal standard).

1,3-Dicarbomethoxy-2-(*t*-butyloxycarbonylamino)isoindoline *cis*-(**3a**) and *trans*-(**3b**), and Dimethyl α-(*t*-Butyloxycarbonylhydrazone)-*o*-benzenediacetate (**6**).

A solution of 7.6 g. (0.02 mole) of *d,l*-dimethyl α,α'-dibromo-*o*-benzenediacetate (**2b**) (4a) and 2.9 g. (0.022 mole) of *t*-butyl carbazate (Merck) in 20 ml. of dimethylformamide was warmed to 50° and 8.4 ml. (0.06 mole) of triethylamine was added dropwise. The resulting mixture was stirred for 3 hours at room temperature, diluted with water to a final volume of 100 ml. and extracted with ether. The residue from the evaporation of the organic layer was chromatographed on silica gel column (25:1), eluting with 98:2 benzene-acetone, to give in succession 0.78 g. of an oil which was triturated with ether to afford 0.33 g. (7%) of **5**, m.p. 203-206° (6). Subsequent elution with 95:5 benzene-acetone gave 2.48 g. (35.6%) of an oil which was identified by nmr as 1:2 mixture of *cis* and *trans* isomers of **3**. This mixture was dissolved in 6 ml. of ether to give, after standing in freezer for a few days, 0.91 g. (13%) of *cis*-**3a**, m.p. 124-126°; ir (nujol): 3330 (NH-CO), 1730 ($COOCH_3$), 1700 (CO-NH) cm^{-1}; nmr (deuteriochloroform): δ 1.42 (s, 9H, 3, CH_3), 3.70 (s, 6H, 2 CH_3CO_2), 5.08 (s, 2H, 2 CH), 6.40 (br. s, 1H, NH), 7.27 (s, 4H, aromatic H).

Anal. Calcd. for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.65; H, 5.93; N, 8.25.

After addition of petroleum ether to the mother liquor, and after long standing in the freezer, 1.44 g. (21%) of *trans*-**3b** was obtained, m.p. 80-83°; ir (nujol): 3360 (NH-CO), 1750 ($COOCH_3$), 1690 (CO-NH) cm^{-1}; nmr (deuteriochloroform): δ 1.42 (s, 9H, 3 CH_3), 3.78 (s, 6H, 2 CH_3CO_2), 5.40 (s, 2H, 2 CH), 6.85 (br. s, 1H, NH), 7.10-7.60 (m, 4H, aromatic H).

Anal. Calcd. for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.38; H, 6.35; N, 7.87.

Finally, 1.7 g. of an oily fraction was collected which by trituration with ether yielded 1.05 g. (15%) of **6**, m.p. 110-112°; ir (nujol): 3325 (NH-CO), 1735 and 1720 (2 $COOCH_3$), 1708 (CO-NH), 1575 (C=N-) cm^{-1}; nmr (deuteriochloroform): δ 1.48 (s, 9H, 3 CH_3), 3.50 (s, 2H, CH_2), 3.60 and 3.82 (2 s, 6H, 2 CH_3CO_2), 7.00-7.60 (m, 4H, aromatic H), 7.90 (br. s, 1H, NH).

Anal. Calcd. for $C_{17}H_{22}N_2O_6$: C, 58.27; H, 6.33; N, 8.00. Found: C, 58.04; H, 6.30; N, 7.91.

Similar treatment of 11.4 g. (0.03 mole) of meso 1,3-dimethyl α,α'-dibromo-*o*-benzenediacetate (**2a**) (4a) afforded 0.35 g. (5%) of **5**, 4.8 g. (46%) of **3** as a mixture (*cis-trans* 1:1), which after crystallization from ether-petroleum ether gave 1.14 g. (11%) of **3a**, and 2 g. (19%) of **6**.

1-Carbomethoxy-4,5-dihydro-3*H*-2,3-benzodiazepin-4-one (**8**).

To 12 ml. of ether saturated with dry hydrogen chloride, 0.5 g. (0.0014 mole) of **6** was added under a nitrogen atmosphere and the mixture was stirred for 1.5 hours at room temperature. Removal of the solvent left a crude product which was crystallized from methanol to give 0.28 g. (90%) of **8**, m.p. 168-169°; ir (nujol): 3280 (NHCO), 1720 ($COOCH_3$), 1680 (CONH), 1570 (C=N-) cm^{-1}; nmr (deuteriochloroform): δ 3.50 (s, 2H, CH_2), 4.00 (s, 3H, CH_3CO_2), 7.10-7.80 (m, 4H, aromatic H), 9.55 (br. s, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.19; H, 4.85; N, 12.51.

1,3-Dicarbomethoxy-2-aminoisoindoline Hydrochloride *cis*-(**4a**) and *trans*-(**4b**).

A solution of 0.5 g. (0.00143 mole) of **3a,b** in ether (5 ml.) was added to 10 ml. of ether saturated with dry hydrogen chloride under a nitrogen atmosphere. After stirring for 1 hour, the crude precipitated hydrochloride was collected by filtration, dried and purified by crystallization from ethanol-ether, to give respectively 52% of **4a** and 29% of **4b**. In the case of **4b**, a recrystallization was required to separate a crop of **4a** and **4b** in admixture (1:1) which could not be resolved by further crystallization.

cis-1,3-Dicarbomethoxy-2-aminoisoindoline Hydrochloride (**4a**).

This compound had m.p. 163-165°; ir (nujol): 3450, 3400, 2720 and 2600 ($N\text{-}NH_3^+$ Cl^-), 1730 ($COOCH_3$) cm^{-1}; nmr (Me_2CO-d_6)): δ 3.75 (s, 8H, 2 CH_3CO_2 + NH_2), 6.02 (s, 2H, 2 CH), 7.46 (s, 4H, aromatic H).

Anal. Calcd. for $C_{12}H_{14}N_2O_4 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 48.73; H, 5.45; N, 9.47; Cl, 11.99. Found: C, 48.46; H, 5.77; N, 9.46; Cl, 12.14.

trans-1,3-Dicarbomethoxy-2-aminoisoindoline Hydrochloride (**4b**).

This compound had m.p. 123-125°; ir (nujol): 3450, 3380, 2700 and 2600 ($N\text{-}NH_3^+$ Cl^-), 1735 and 1710 ($COOCH_3$) cm^{-1}; nmr (Me_2CO-d_6): δ 2.35-2.90 (br. s, 2H, NH_2), 3.82 (s, 6H, 2 CH_3CO_2), 5.85 (s, 2H, 2 CH), 7.45 (s, 4H, aromatic H).

Anal. Calcd. for $C_{12}H_{14}N_2O_4 \cdot 2HCl \cdot 2H_2O$: C, 44.65; H, 5.93; N, 8.68; Cl, 10.98. Found: C, 44.28; H, 5.57; N, 8.93; Cl, 11.35.

1,3-Dicarbomethoxy-2-nitrosoisoindoline *cis*-(**10a**) and *trans*-(**10b**).

A stirred suspension of 10 g. (0.036 mole) of 1,3-dicarbomethoxyisoindoline (**9a,b**) as the hydrochloride in 60 ml. of 2*N* hydrochloric acid was cooled to 0°, and a solution of 3.6 g. (0.052 mole) of sodium nitrite in 20 ml. of water was added dropwise over 20 minutes. After complete addition, the mixture was stirred at room temperature for 5 hours. The product was filtered, washed and dried to give the crude 2-nitrosoisoindoline **10**, which was crystallized from methanol to afford 78% of **10a**, and 86% of **10b**, respectively.

cis-1,3-Dicarbomethoxy-2-nitrosoisoindoline (**10a**).

This compound had m.p. 116-117°; ir (carbon tetrachloride): 1770 and 1740 ($CO\text{-}OCH_3$), 1460 and 1430 (N-NO) cm^{-1}; nmr (deuteriochloroform): δ 3.70 and 3.80 (2 s, 6H, 2 CH_3CO_2), 5.80 and 6.50 (2 s, 2H, 2 CH), 7.40-7.80 (m, 4H, aromatic H).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.38; N, 10.60. Found: C, 54.72; H, 4.46; N, 10.48.

trans-1,3-Dicarbomethoxy-2-nitrosoisoindoline (**10b**).

This compound had m.p. 102-104°; ir (carbon tetrachloride): 1760 and 1750 ($COOCH_3$), 1460 and 1430 (N-NO) cm^{-1}; nmr (deuteriochloroform): δ 3.70 and 3.82 (2 s, 6H, 2 CH_3CO_2), 5.75 and 6.53 (2 s, 2H, 2 CH), 7.40-7.70 (m, 4H, aromatic H).

Anal. Calcd. for $C_{12}H_{12}N_2O_5$: C, 54.54; H, 4.38; N, 10.60. Found: C, 54.68; H, 4.51; N, 10.70.

Catalytic Reduction of **10a,b**.

A suspension of 0.5 g. (0.0019 mole) of **10a** in 10 ml. of absolute ethanol and 0.13 g. of 10% palladized charcoal was hydrogenated at room temperature and atmospheric pressure. After 7 hours, the uptake of hydrogen (~ 110% theoretical) ceased, the suspension was filtered and the residue washed with ethanol. The filtrate was concentrated to dryness *in vacuo* and the resulting residue was triturated with ether yielding in succession 0.04 g. (9%) of **5**, and 0.08 g. of a product identified by nmr as a ~ 1:1 mixture of **5** and **9a**. Finally, the clear solution was treated with hydrogen chloride in ether to give 0.3 g. (58%) of **9a** (m.p., ir and nmr spectra were superimposable) as the hydrochloride, m.p. 158-162°.

Using the above procedure, from 2 g. (0.0076 mole) of **10b** were obtained 0.53 g. (30%) of **5**, 0.25 g. of a mixture ~ 1:1 of **5** and **9a** and finally 0.94 g. (45.6%) of **9a**.

Reduction of **10a,b** with Zinc and Acetic Acid.

To a stirred suspension of zinc dust (0.9 g., 0.0138 mole) in 2:1 acetic acid-water (20 ml.) **10a,b** (1 g., 0.00378 mole) was added in portions at room temperature. The mixture was heated to 40° for 1 hour when a further portion of zinc dust (0.6 g., 0.0092 mole) was added. After stirring for an additional 30 minutes the reaction mixture was cooled; the excess zinc was filtered and washed with *N* hydrochloric acid (5 ml.). The filtrate was basified with concentrated ammonia and, after removal by filtration of the precipitated **5**, extracted with ether. The organic layer was dried (sodium sulfate) and evaporated; the oily residue was chromatographed on silica gel column (50:1) eluting with benzene to give in succession an additional portion of **5** and **4a** as an oil. The latter treated with hydrogen chloride in ether afforded the hydrochloride salt, which was purified by crystallization from ethanol-ether. Compound **10a** gave 41% of **5** and 10% of **4a**; **10b** gave 16% of **5** and 25% of **4a**.

1,3-Dicarbomethoxy-2-(phenylmethylimino)isoindoline *cis*-(**11a**) and *trans*-(**11b**).

To a cooled (0-5°) suspension of 5 g. of zinc dust in 10 ml. of water a solution of 4 g. (0.015 mole) of **10a,b** in glacial acetic acid (22 ml.) was added. The mixture was stirred at room temperature for 1 hour, the excess zinc was filtered and 1.75 g. (0.0165 mole) of benzaldehyde was slowly added. After stirring for an additional 1 hour, the crude 2-phenylmethylimino derivate **11** was collected by filtration and purified by crystallization from methanol to yield, respectively, **11a** (68%) and **11b** (45%).

cis-1,3-Dicarbomethoxy-2-(phenylmethylimino)isoindoline (**11a**).

This compound had m.p. 105-106°; ir (nujol): 1760 and 1735 ($COOCH_3$) cm^{-1}; nmr (deuteriochloroform): δ 3.85 (s, 6H, 2 CH_3CO_2), 5.50 (s, 2H, 2 CH), 7.20-7.70 (m, 10H, 9 aromatic H + CH=N-).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.46; H, 5.21; N, 8.37.

trans-1,3-Dicarbomethoxy-2-(phenylmethylimino)isoindoline (**11b**).

This compound had m.p. 137-139°; ir (nujol): 1745 and 1730 ($COOCH_3$) cm^{-1}; nmr (deuteriochloroform): δ 3.72 (s, 6H, 2 CH_3CO_2), 5.70 (s, 2H, 2 CH), 7.20-7.70 (m, 10H, 9 aromatic H + CH=N-).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.32; H, 5.39; N, 8.35.

Attempted Conversion of **3a,b** to **6**.

To a solution of 0.5 g. (0.0014 mole) of **3a,b** in 2.5 ml. of dimethylformamide warmed to 50°, 0.22 ml. (0.16 g., 0.0015 mole) of triethylamine was added. The mixture was stirred at room temperature for 3 hours, and then worked up as reported for the synthesis of **3** to give 0.5 g. of starting **3a,b** contaminated (tlc, uv and nmr analyses) by **5**, approximately 5%.

REFERENCES AND NOTES

(1) Also to be considered Part X in the series Researches on Isoindole Derivatives. Part IX: G. Cignarella, F. Savelli and P. Sanna, *Syn-*

thesis, 252 (1975).

(2) Present address: Institute of Pharmaceutical Chemistry of the University, via Benedetto XV 3, 16132 Genova, Italy.

(3) G. Cignarella, P. Sanna, E. Miele, V. Anania and M. S. Desole, *J. Med. Chem.*, in press.

(4a) G. Cignarella and A. Vigevani, *Gazz. Chim. Ital.*, **98**, 1474 (1968); (b) G. Cignarella, F. Savelli, R. Cerri and P. Sanna, *J. Heterocyclic Chem.*, **11**, 1049 (1974).

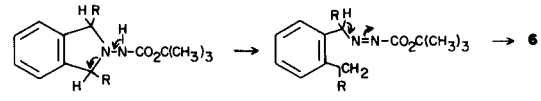
(5) L. A. Carpino, *J. Am. Chem. Soc.*, **79**, 4427 (1957).

(6) G. Cignarella and G. G. Gallo, *Gazz. Chim. Ital.*, **99**, 1115, (1969).

(7) G. Cignarella and A. Saba, *ibid.*, **99**, 450 (1969).

(8) The isomers **3a,b** when heated in dimethylformamide in the presence of triethylamine decomposed in little extent to **5** (see Experimental).

(9) A referee suggested that **6** could be formed by a reverse electron shift of **3** followed by a double bond migration, as depicted below.



However, this hypothesis is not supported by the behaviour of **3** under the reaction conditions leading to **6** (8).