On the Behavior of α-Brominated Dimethyl *o*-Benzenediacetate Toward Nitrogen Nucleophiles (1). Part I. Reaction of Dimethyl α,α'-Dibromo *o*-Benzenediacetate with Hydrazines.

G. Cignarella, F. Savelli, R. Cerri and P. Sanna

Institute of Pharmaceutical Chemistry of the University, 07100 Sassari, Italy

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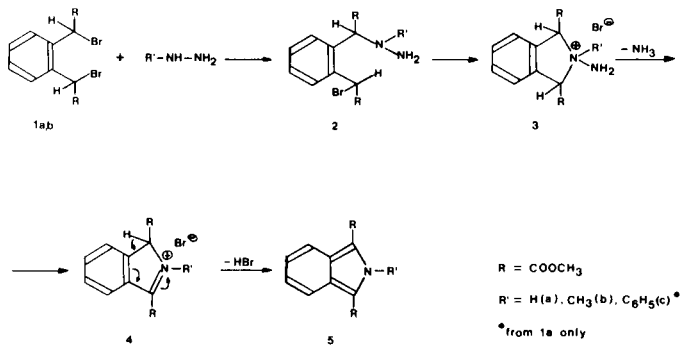
Meso- (**1a**) and racemic dimethyl α,α'-dibromo *o*-benzenediacetate (**1b**) when condensed with hydrazine and methylhydrazine furnished respectively 1,3-dicarbomethoxyisoindole (**5a**) and its *N*-methyl derivative (**5b**). Reaction of phenylhydrazine with **1a** led to the *N*-phenylisoindole (**5c**) and to the *N*-anilino isoindoline (**6**) as the *cis* isomer; conversely, **1b** was transformed into a mixture of the 2-phenyl-1,2,3,4-tetrahydrophthalazine (**7**), the *trans* isomer of (**6**), the *N*-anilino-isoindole (**5d**) and dimethyl α-(*N'*-phenylhydrazino)-*o*-benzenediacetate (**8**). Compounds **1a** and **1b** were also condensed with acetylhydrazine to give a mixture of the *N*-acetylaminoisoindoline (**12**) and of the 2-acetyl-1,2,3,4-tetrahydrophthalazine (**13**).

In a continuing interest in the behavior of α,α'-dibromo-*o*-benzenediacetic acid towards nucleophiles, its dimethyl ester (**1**) (2a) as the *meso* (**1a**) and the *racemic* (**1b**) diastereoisomer was allowed to react with hydrazine and monosubstituted hydrazines. Accordingly, **1a** and **1b** were condensed with hydrazine hydrate in refluxing methanol to give unexpectedly 1,3-dicarbomethoxyisoindole (**5a**), m.p. 206-208°, as the sole reaction product, identified by comparison with an authentic sample (2c). A similar result was obtained with methylhydrazine at room temperature, the known (2c) 1,3-dicarbomethoxy-*N*-methylisoindole (**5b**), m.p. 143-145°, being isolated in about 70% yield.

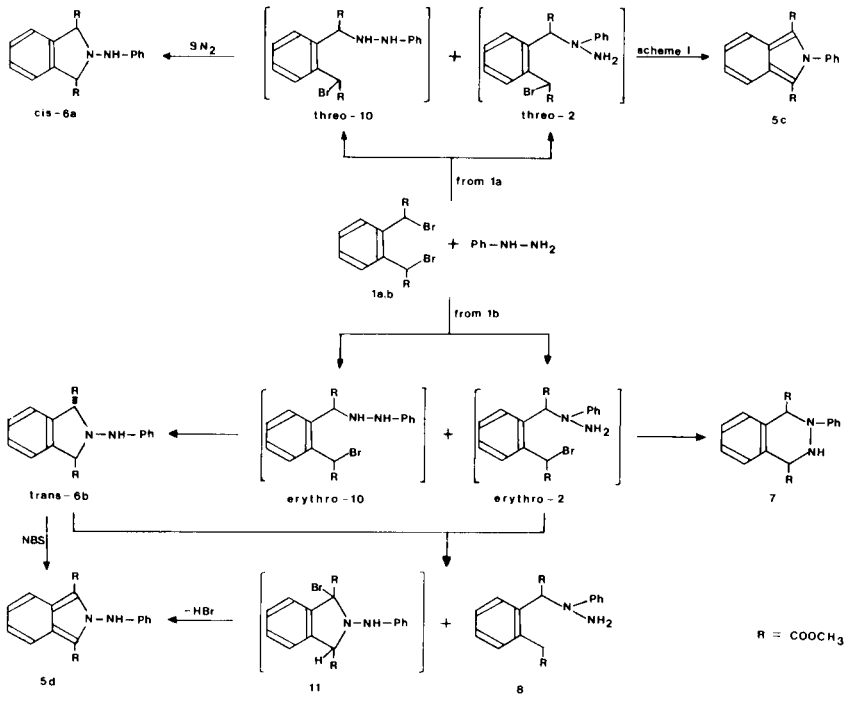
SCHEME I



Phenylhydrazine behaves differently towards **1a** and **1b** also giving rise to a mixture of products. Thus, by allowing **1a** and phenylhydrazine (molar ratio 1:3) to reflux in benzene we isolated in addition to 37% of the known (2d) 2-phenyl-1,3-dicarbomethoxyisoindole (**5c**), m.p. 200-201°, about 35% of a solid, m.p. 135-137° identified as *cis*-2-anilino-1,3-dicarbomethoxyisoindoline (**6a**). The structure **6** was preferred to that of the isomeric tetrahydrophthalazine (**7**) on the basis of nmr evidences (the methine CH appeared as a singlet at 5.2 δ) and of ir analogies with known isoindolines (2a,b). On the contrary, *racemic* **1b** under identical reaction conditions led to a more complex mixture from which we were able to isolate *trans*-2-anilino-1,3-dicarbomethoxyisoindoline (**6b**), m.p. 94-95° (27%), 1,2,3,4-tetrahydro-2-phenyl-1,5-dicarbomethoxyphthalazine (**7**), m.p. 164-165° (33%), 2-anilino-1,3-dicarbomethoxyisoindole (**5d**), m.p. 155-156° (7%) and dimethyl α-(N_1-phenylhydrazino)-*o*-benzenediacetate (**8**), m.p. 140-142° (5.5%).

The structure of **6b** was identified by ir and nmr spectra, while its *trans* configuration was suggested by the downfield nmr shift of the methine hydrogens (2b) (5.38 δ) in respect to that of the *cis* isomer (5.20 δ). Tetrahydrophthalazine **7** was identified on the basis of the nmr spectrum which exhibited two singlets at 4.65 and 5.25 δ attributed to the methine hydrogens, while the aliphatic NH appeared as a broad singlet at 5.06 δ, upfield in respect to that of the aromatic NH of the *N*-anilino-isoindoline **6** (6.20 δ). The isoindole structure of **5d** was proved by uv and nmr analogies with known 1,3-dicarbo-

SCHEME II



methoxyisoindoles (2c,d) while compound **8** was found to be identical with an authentic sample prepared by condensing dimethyl α-bromo-*o*-benzenediacetate (**9**) with phenylhydrazine at room temperature (3).

The isolation of isoindoles **5** in the condensation of **1** with hydrazine or methyl- and phenylhydrazine can be explained (see Scheme I) through the formation of an isoindolinium salt (**3**) derived by an initial S_N2 substitution of one of the bromine-bearing carbons of **1** with the hydrazine N-1 followed by an internal quaternization of the thus formed **2**. The mobility of the methine hydrogens caused **3** to be unstable with consequent loss of ammonia to give an indoleninium salt (**4**) which eventually evolved to **5** by deprotonation. The failure of **1b** to give 2-phenylisoindole **5c**, which conversely was isolated from **1a**, seems connected with the *erythro* configuration of the intermediate **2**. Models examination showed in fact that while in *threo*-**2** quaternization to **3** is favored, in the *erythro* form the backside attack of the hydrazine N-1 to the bromine-bearing carbon is more hindered than that of the hydrazine N-2, cyclization to **7** being therefore preferred to quaternization. The mechanisms involved in the reactions of **1a** and **1b** with phenylhydrazine are rationalized in scheme II. The formation of the isoindolines **6a** and **6b** respectively from **1a** and **1b** might occur through and initial S_N2 mono alkylation on the phenylhydrazine N-2 (4) to give respectively *threo* (**10**) and *erythro* (**10**) which by successive intramolecular S_N2 alkylation on the same hydrazine nitrogen cyclized to **6**. The unexpected formation of **5d** and **8** could be at first glance attributed for **5d** to a dehydrogenation of isoindoline **6** by autoxidation or by the action of phenylhydrazine; for **8**, to the presence in the starting **1b** of dimethyl α-bromo-*o*-benzenediacetate (**9**) as a possible contaminate, the former being synthetized by bromination of dimethyl-*o*-benzenediacetate with *N*-bromosuccinimide (7). However, both hypotheses were ruled out because of the experimented stability of **6** both under oxygenated atmosphere and toward phenylhydrazine, and respectively because of the high solubility of oily **9** in the crystallization solvent (methanol) of **1b**.

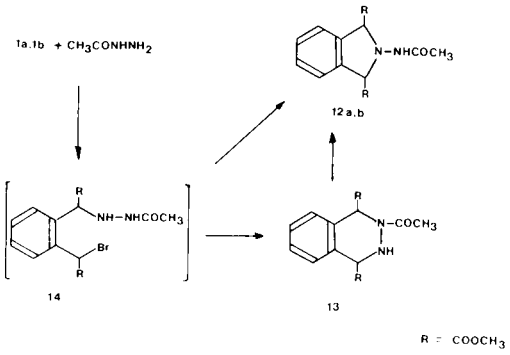
On the contrary, the formation of **5d** and **8** could be caused by a transbromination between *erythro*-**2** and **6** to give respectively **8** and the unstable bromoisoindoline **11** which evolved to isoindole **5d** by loss of hydrogen bromide. This hypothesis, which also gives account of the comparable yields of the two products (5.5% and 7%), seems supported by the observed isolation of **5d** in 70% yield by bromination of **6b** with *N*-bromosuccinimide.

The lack of **5b** and **8** in the reaction mixture from **1a** and phenylhydrazine could be explained on the basis of the rapid quaternization of *threo*-**2** to **5c** whose formation from the *erythro* diastereoisomer is on the contrary sterically disfavored.

Finally, **1a** and **1b** were allowed to react with acetylhydrazine in refluxing methanol. Both diastereoisomers behaved similarly, being transformed respectively into 34% and 14% of *trans*-2-acetylamino-1,3-dicarbomethoxyisoindoline (**12b**), m.p 150-152°, contaminated by about 20% (nmr analysis) of the *cis* isomer (**12a**), and into 48% and 41% of 1,2,3,4-tetrahydro-2-acetyl-1,4-dicarbomethoxyphthalazine (**13**). Besides them, about 20% of **1** as a mixture of **1a** + **1b** and 10% of isoindole **5a** were isolated The separation of the reaction products was accomplished by silica gel chromatography eluting with chloroform. This procedure however did not separate **12a** from **12b**, as well as the repeated crystallizations of **12** from methanol.

The structure of **13** was suggested by ir absorption at 3260 cm^{-1} (amine NH) and by the nmr signal at 7.5 δ rapidly exchangable with deuterium oxide. In comparison, ir and nmr analyses of the isomeric **12**, revealed the presence of the acetylamino group (absorption at cm^{-1} 3420 (amide NH), 1680 and 1480 (-CONH-): broad singlet at 8.30 δ slowly exchangeable with deuterium oxide). The nmr spectrum of the isomeric mixture **12** also showed the signals of the methine hydrogens as two singlets at 5.68 δ (*trans*) and at 5.20 δ (*cis*), integrated in a ratio ~ 80:20.

SCHEME III



Contrary to the mechanism hypothesized for the aryl derivatives **6** and **7**, the known alkylation at the *N*-2 of acetylhydrazine in neutral medium (8) suggested that the synthesis of **12** and **13** might occur through the common intermediate **14** by a further intramolecular alkylation at the acylated or non-acylated nitrogen. In the latter case the isolation from **1a** and **1b** of an isomeric mixture of *cis* and *trans* **12** can be attributed to a preliminary base induced *meso* ⇌ *racemic* equilibration of the starting **1**, which was supported by the recovery of unreacted **1** actually composed of both the diastereoisomers (ir and nmr analyses) (2a). As a consequence, the reasonable hypothesis of the double S_N2 mechanism involved in the condensation of **1** with acetylhydrazine to give **12** accounted for the isolation of *cis* **12a** and *trans* **12b** respectively from **1a** and **1b** both present after equilibration.

However the proposed pathway, even if the main one, did not seem the one involved. We have in fact observed that tetrahydrophthalazine **13** when refluxed for 24 hours in methanol and equimolar acetylhydrazine underwent a ring contraction to **12**, although in a moderate extent (~ 15%). In addition, about 15% of the isoindole **5a** was separated by column chromatography.

Since to our knowledge the only example of a ring contraction of a 1,2,3,4-tetrahydrophthalazine is the transformation in refluxing hydrazine of the 4-oxo derivative into *N*-aminophthalimide (9), further research, which is in progress, on the chemistry of **12** and **13** is needed to shed more light on the reaction conditions which favored the rearrangement (10) as well as the decomposition to isoindole **5a**.

EXPERIMENTAL

Ir spectra were determined with a Perkin Elmer Model 157/G spectrophotometer; nmr spectra were obtained in deuteriochloroform by means of a Varian A-60 spectrometer with tetramethylsilane as the internal standard.

Reactions of **1a** and **1b** with Hydrazines.

Hydrazine Hydrate Affording 1,3-Dicarbomethoxyisoindole (**5a**).

A mixture of 3.8 g. (0.01 mole) of **1a** and 1.5 g. (0.03 mole) of hydrazine hydrate in 30 ml. of methanol was refluxed for 6 hours. The solution was concentrated and the precipitate was filtered and washed with water, to give 1.58 g. (66%) of **5a**, m.p. 206-208° (2c). Similarly treated *racemic*-**1b** gave **5a** in 63% yield.

Methylhydrazine Affording 2-Methyl-1,3-dicarbomethoxyisoindole (**5b**).

To a solution of 5 g. (0.0132 mole) of **1a** in 50 ml. of benzene, 1.82 g. (0.0396 mole) of methylhydrazine was added and the mixture was stirred at room temperature for 24 hours. The methylhydrazine hydrobromide (2.92 g., 89%) was filtered, the filtrate was evaporated and the solid residue was crystallized from methanol to give 2.4 g. (70%) of **5b**, m.p. 143-145° (2c).

Similarly treated, *racemic*-**1b** gave **5b** in 67% yield.

Phenylhydrazine with **1a** Affording 2-Phenyl-1,3-dicarbomethoxyisoindole (**5c**) and *cis*-2-Anilino-1,3-dicarbomethoxyisoindoline (**6a**).

A mixture of 10 g. (0.0264 mole) of **1a** and 8.55 g. (0.0792 mole) of phenylhydrazine in 80 ml. of benzene was refluxed for 24 hours. The phenylhydrazine hydrobromide (8 g., 81%) was filtered, the filtrate was washed with 5% hydrochloric acid and the organic layer was dried over sodium sulphate and evaporated. The residue was triturated with 30 ml. of methanol and the precipitate was filtered and crystallized from benzene to give 3 g. (37%) of **5c**, m.p. 200-201° (2d). The methanol solution was concentrated to give 3 g. (35%) of **6a**, m.p. 135-137° (methanol); ir (nujol): 3280 (NH), 1765 and 1715 (ester) cm^{-1}; nmr: δ 3.75 (s, 6H,

$2COOCH_3$), 5.20 (s, 2H, 2CH), 6.18 (broad singlet which disappeared after deuteration, 1H, NH) 6.75-7.40 (m, 9 aromatic H).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.04; H, 5.46; N, 8.81.

Phenylhydrazine with **1b** Affording 1,2,3,4-Tetrahydro-2-phenyl-1,4-dicarbomethoxyphthazine (**7**), *trans*-2-Anilino-1,3-dicarbomethoxyisoindoline (**6b**), 2-Anilino-1,3-dicarbomethoxyisoindole (**5d**) and Dimethyl(α-N_1-phenylhydrazino)-*o*-benzenediacetate (**8**).

A mixture of 30.4 g. (0.08 mole) of **1b** and 25.9 g. (0.24 mole) of phenylhydrazine in 200 ml. of benzene was refluxed for 24 hours. The phenylhydrazine hydrobromide (25 g., 82%) was filtered off, the filtrate was washed with 5% hydrochloric acid, the organic layer was dried over sodium sulphate and the solvent was evaporated. The oily residue was triturated with 40 ml. of ether and the precipitate was filtered to give 8.8 g. (33%) of **7**, m.p. 164-165° (benzene); ir (nujol): 3160 (NH) and 1720 (ester) cm^{-1}; nmr: δ 3.60 (s, 6H, $2COOCH_3$), 4.68 (s, 1H, CH), 5.26 (s, 1H, CH), 5.05 (centered) (broad signal which disappeared after deuteration 1H, NH) 6.70-7.44 (m, 9 aromatic H).

The ether filtrate from **7** was concentrated *in vacuo* until separation of a solid product (3.7 g.) which was filtered and chromatographed over silica gel (20:1) eluting with benzene to give in succession 1.81 g. (7%) of **5d**, as yellow needles, m.p. 155-156° (methanol) and 1.45 g. (5.5%) of **8**, m.p. 140-143° (methanol). The analytical data of **5d**: ir (nujol): 3320 (NH), 1725 and 1675 (ester) cm^{-1}; nmr: δ3.82 (s, 6H, $2COOCH_3$), 6.4-8.2 (m, 9 aromatic H), 9.10 (broad singlet which disappeared after deuteration, 1H, NH).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.98; H, 5.14; N, 8.73.

The analytical data of **8**: ir (carbon tetrachloride): 3460, 3375, 3270 ($N\text{-}NH_2$), 1740 (ester) cm^{-1}; nmr: δ 3.50 (s, 3H, $COOCH_3$), 3.62 (d, 2H, CH_2), 3.75 (s, 3H, $COOCH_3$), 5.95 (s, 1H, CH), 6.7-7.4 (m, 9 aromatic H), 3.60 (centered) (broad signal which disappeared after deuteration 2H, NH_2).

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.43; H, 6.06; N, 8.59.

The ether filtrate was evaporated and the oily residue was dissolved in 30 ml. of methanol. After standing in a refrigerator for a few days, 7.3 g. (27%) of **6b**, m.p. 94-95° (methanol), was separated: ir (nujol): 3295 (NH), 1725 (ester) cm^{-1}; nmr: δ 3.75 (s, 3H, $COOCH_3$), 5.38 (s, 1H, CH), 6.2 (broad signal which disappeared after deuteration, 1H, NH), 6.70-7.40 (m, 9 aromatic H).

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.98; H, 5.77; N, 8.75.

Acetylhydrazine with **1a** or **1b** Affording 2-Acetylamino-1,3-dicarbomethoxyisoindoline **12** and 1,2,3,4-Tetrahydro-2-acetyl-1,4-dicarbomethoxyphthalazine **13**.

A solution of 3.8 g. (0.01 mole) of **1a** and 2.2 g. (0.03 mole) of acetylhydrazine in 50 ml. of methanol was refluxed for 18 hours. The solvent was evaporated, the residue was treated with water and the insoluble was extracted with chloroform. The residue from the evaporation of the organic layer was chromatographed on silica gel eluting with chloroform, to give in succession 0.72 g. (19%) of a mixture of **1a** and **1b**, m.p. 90-94° (ir and nmr analyses) (2a), 0.19 g. (8%) of **5a**, m.p. 203-205°, 1.41 g. (48%) of **13**, m.p. 129-131° (methanol) and 1 g. (34%) of **12**, m.p. 150-152° (methanol). Although the latter compound exhibited a single spot on tlc (silica gel, mobil phase chloroform-acetone 80:20), its nmr revealed the presence of a mixture of the *cis* and *trans* isomers (~ 1:4). Repeated crystallizations from methanol did not modify the isomeric composition. The analytical data of **12**: ir (chloroform): 3420 (NH), 1755 (ester), 1680 and 1480 (sec. amide CO) cm^{-1}; nmr: δ 1.98 (s) and 2.40 (s) (3H, $COCH_3$), 3.84 (s, 6H, $2COOCH_3$), 5.10 (s) and 5.66 (s) (2H, 2CH), 7.2-7.6 (m, 4 aromatic H), 8.30 (broad singlet which disappeared after deuteration, 1H, NH). The signals at δ 2.40 and 5.10 were attributed to the presence of about 20% of the *cis* **12**.

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C.57.41; H, 5.53; N, 9.74.

The analytical data of **13**: ir (chloroform): 3260 (NH), 1740 (ester), 1600 (tert. amide CO) cm^{-1}; nmr: δ 2.32 (s, 3H, $COCH_3$), 3.82 (broad singlet, 6H, $2COOCH_3$), 5.30 (broad singlet, 2H, 2CH), 7.3-7.5 (m, 4 aromatic H + NH) (integration for 4H after dueteration).

Anal. Calcd. for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.57; H, 5.54; N, 9.81.

Similarly treated, *racemic* **1b** afforded 10% of **5a**, 14% of **12** (*cis-trans* mixture ~ 1:4) and 41% of **13** besides 16% of a mixture of **1a** + **1b**.

Aromatization of **6b** to **5d**.

A solution of 0.23 g. of **6b** in 10 ml. of carbon tetrachloride was treated with 0.126 g. of *N*-bromosuccinimide and the mixture was stirred for 6 hours under irradiation with a 300 watt lamp. After filtration of the succinimide, the solution was evaporated to dryness and the residue was triturated with methanol to give 0.18 g. of **5d** contaminated with about 15% of **5a** which was separated because of the poor solubility of the latter in hot methanol.

Attempted Isomerization **13** → **12**.

A solution of 0.58 g. of **13** and 0.15 g. of acetylhydrazine in 5 ml. of methanol was refluxed for 24 hours. Tlc analysis of the solution revealed the presence of isoindole **5a** and of **12** after 7 hours. After removal of the solvent the residue was treated with water and extracted with chloroform. The organic layer was dried and the solvent was evaporated to give 0.55 g. of a solid which was chromatographed on silica gel eluting with chloroform and collecting in succession 0.066 g. (15%) of **5a**, 0.30 g. of unreacted **13** and 0.093 g. (16%) of **12**, m.p. 148-150°. The latter examined by nmr without further purification was found composed of about 85% of *trans* **12b** and 15% of *cis* **12a**.

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(3) G. Cignarella, R. Cerri and F. Savelli, *J. Heterocyclic Chem.*, to be published.

(4) Contrasting data are reported in the literature (5) on the nitrogen involved in the mono alkylation of phenylhydrazine. In spite of a current opinion (6) we have gained experimental evidence of a preferential *but not exclusive* alkylation of the phenyl-bearing nitrogen. In any case, the substitution on both nitrogens seems driven by steric factors when bulky halogenides like **1** are employed.

(5) R. L. Hinman, *J. Org. Chem.* **23**, 1587 (1958) and reference reported therein.

(6) P. A. S. Smith, in "Open-Chain Nitrogen Compounds", W. A. Benjamin, Inc., New York-Amsterdam, 1966, Vol. II, p. 127.

(7) G. Cignarella, A. Saba and A. Maselli, *Ann. Chim. (Rome)*, in press.

(8) See ref. 6, p. 179.

(9) E. Bellasio and E. Testa, *Il Farmaco, Ed. Sci.*, **25**,305 (1970).

(10) Such a rearrangement did not seem to occur for the *N*-phenyl derivative **7** because of its stability toward phenylhydrazine in a refluxing benzene solution.