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THE REACTION OF α-CHLORO-α,α-DIPHENYLACETAMIDES WITH POTASSIUM N-CYANOANILIDE

A NOVEL TYPE OF *CINE* SUBSTITUTION[a]

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Abstract—Three types of products are formed in the reactions of α-chloro-α,α-diphenylacetamides (**1a–c**) with potassium N-cyanoanilide: *cine* substitution products of type **2** as the main products, and two types of normal products (**4a** and **b**, and **3**, **6** and **7a**, respectively) whose formation reflects the ambident reactivity of the N-cyanoanilide anion.

As part of our studies into the reactions of cyanoamide anions with halogen derivatives of different classes of organic compounds we have recently investigated the reactions of α-chloro-α,α-diphenylacetamides (**1a–c**) with potassium N-cyanoanilide.

When equimolecular mixtures of **1a**[2] and potassium N-cyanoanilide reacted in dry DMSO, and were subsequently treated with H_2O, considerable amounts of benzilamide (the hydrolysis product of unreacted **1a**) were obtained in addition to 24 per cent of **2a**. While **1a** reacted slowly with N-cyanoanilide anion, it was rapidly hydrolysed in DMSO solution under neutral conditions. In the presence of a threefold excess of potassium N-cyanoanilide the yield of **2a** was raised to 38% but no benzilamide could be isolated from the strongly alkaline solution. Minor amounts of 5 - imino - 1,4,4 - triphenyl - 2 - imidazolidinone (**3**)[3] and of 1,5,5-triphenylglycocyamidine (**4a**)[3] were obtained as the by-products in both cases.

The structure of **2a** was established by a two-step conversion into **5b** which proved identical with an authentic sample prepared starting with **5c**.[4] Similar anomalous *p*-substituted products were obtained[5,6] by reacting N-substituted derivatives of **1a** with (mostly cyclic) secondary amines.

Several additional products, formed in trace amounts, such as N,N'-dibenzhydrylurea, N-benzhydryl-N'-phenylurea and N-(1-cyanobenzhydryl)-N'-phenylurea (**6**)[3] could be isolated in part of the experiments. The latter might well be the precursor of **3** since, on alkaline treatment, it readily transforms into **3**.[3]

When **1b**[6] reacted with a threefold excess of potassium N-cyanoanilide in anhydrous DMSO, trace amounts of 3 - (t - butyl) - 1,5,5 - triphenylglycocyamidine (**4b**)[7] and of 3 - (t - butyl) - N(2),5,5 - triphenylglycocyamidine (**7a**) were isolated in addition to 45% of **2b**. The structure of **2b** was established by degradation to **5b** (as in the case of **2a**). The structure assignment of **7a** is based on the observations that (1) **7a**, when refluxed with 48% hydrobromic acid, is converted into N(2),5,5-triphenylglycocyamidine (**7b**), (2) the t-Bu group of **7a** is, according to its chemical shift, attached to N(3) rather than to N(1) (Tables 1 and (3), the t-Bu group of **7a** is eliminated on electron impact in the form of isobutylene (causing the M-56 peak to become the base peak of the mass spectrum) which is consistent with its attachment to N(3) rather than to N(1).[8] (The mass spectra of 1 - (t - butyl) - 5,5 - diphenylglycocyamidines, in contrast, exhibit abundant M-57 peaks.[8])

1c[10] and a threefold excess of potassium N-cyanoanilide in anhydrous DMSO furnished 15–35% of **2c**. Similar results were obtained when the reaction was performed in refluxing acetone; in the latter case considerable amounts of what appears to be a mixture of polymeric products was also formed. The proof of structure of **2c** was similar to that of **2a** and **b**.

In contrast to the product formed in the reaction of **1a** and sodium N-cyanoamide,[11] formation of the products **2–4** and **6–7** does not require an aziridinone of type **8**. The compounds **2** are probably *not* formed *via* compounds **8** since (1) the formation of a type **8** intermediate is not possible in the *c* series and (2) since the complex mixtures formed when DMSO solutions of separately prepared **8a**[12] were reacted with alkali N-cyanoamides, did not contain type **2** products even in trace amounts.[9,*] Investigations with the aim of elucidating the pathway leading to the formation of the type **2** *cine* products are in progress.

Compounds **3**, **4**, **6** and **7**, on the other hand, may be envisaged as derivatives of initially formed normal nucleophilic substitution products (**9** and **10**, respectively) of the starting compounds. The formation of two series of products reflects the double reactivity of the N-cyanoanilide anion, *cf.*[13] The exchange of 1 molecule of water between the functional groups of **9** in the course of the reaction leading to **6** is rather peculiar.

An alternative pathway of formation of **10** (R = t-Bu,

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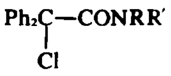
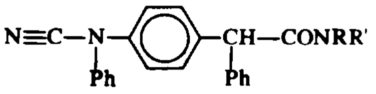
[a] Part of the present work has been published in a preliminary communication, see Ref.[1]

*For the reaction of **8a** with N-cyanoamines, *cf.* Ref.[7]



$Ph_2C(Cl){-}CONRR'$

1



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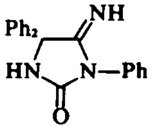
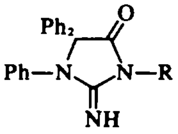


3

a: R = R′ = H
b: R = *t*-Bu, R′ = H
c: R = R′ = Me



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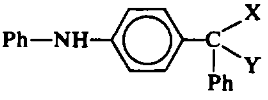
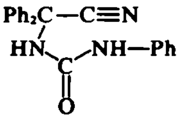
a: R = H*
b: R = *t*-Bu



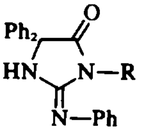
5

a: X = COOH, Y = H
b: X = Y = H
c: X + Y = O

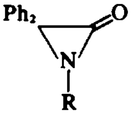


$Ph_2C(C{\equiv}N){-}NH{-}C(=O){-}NH{-}Ph$

6

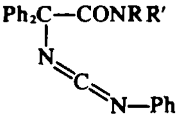


7*



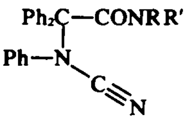
8

a: R = *t*-Bu
b: R = H



$Ph_2C(N{=}C{=}N{-}Ph){-}CONRR'$

9

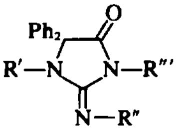


$Ph_2C(N(Ph){-}C{\equiv}N){-}CONRR'$

10

*Potentially tautomeric compounds. Their actual tautomeric structures have not been determined.

Table 1. NMR spectra of some 5,5-diphenylglycocyamidines



(Solvent: $CDCl_3$, Ref: TMS, δ scale)

R′	R″	R‴	Ref.	Chemical shift 1-(t-Bu)	Chemical shift 3-(t-Bu)
t-Bu	H	H	[9]	1·31	—
Me	H	t-Bu	[7]	—	1·75
t-Bu	H	t-Bu	[7]	1·30	1·67
H	CPh_2-CONH(t-Bu)	t-Bu	[9]	—	1·87
Compound **7a**				—	1·80

R′ = H) which, at present, cannot be ruled out, could involve the intermediacy of **8a** since the latter is known[7] to furnish the required product with N-cyanoaniline (liberated from its potassium salt by protons formed as the by-products of reaction **1b**→**8a**). An analogous pathway may be operative in the course of formation of **10** (R = R′ = H) as well.

EXPERIMENTAL

Preparation of α-chloro-α,α-diphenylacetamides **1b** *and* **c**

(a) A mixture of t-butylamine (1·38 g; 19 mmole), triethylamine (1·91 g; 19 mmole) and dichloromethane (20 ml) was added by drops under ice cooling and continuous stirring within about 1/2 h to a soln of α-chloro-α,α-diphenylacetyl chloride (5·0 g; 19 mmole) in dichloromethane (20 ml). The resulting soln was stirred for another 4 h and extracted with 1 N HCl (two portions, 40 ml each), 1 N NaOH and water (40 ml, each), dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from a small amount of gasoline to yield 3·7 g (65%) of **1b**, m.p. 92–93° (gasoline), lit.[6] m.p. 91–93°. No experimental details are given in Ref. 6. (Found: C, 71·47; H, 6·86; Cl, 11·68; N, 4·64. $C_{18}H_{20}ClNO$ (301·82) requires: C, 71·63; H, 6·68; Cl, 11·75; N, 4·64%).

(b) A stream of dimethylamine, liberated from an aqueous (30 ml) soln of its hydrochloride (9·3 g; 0·114 mole) with 10% NaOH aq and dried over NaOH, was introduced within 1 h under ice-cooling and continuous stirring into a soln of α-chloro-α,α-diphenylacetyl chloride (10 g; 37·7 mmole) in dry chloroform (150 ml). The mixture was stirred for another 2 h at 0° and worked up as described under (a) to yield 6·4 g (62%) of **1c**, m.p. 121–122° (gasoline), lit.[10] m.p. 122–123°. (Found: Cl, 12·95; N, 5·12. $C_{16}H_{16}ClNO$ (273·76) requires: Cl, 12·71; N, 5·05%). Compound **1c** has earlier been prepared[10] from diphenyl ketene.

Reactions of α-chloro-α,α-diphenylacetamides **1a–c** *with potassium N-cyanoanilide*

(a) The soln of **1a**[2] (4·0 g; 16 mmole) and potassium N-cyanoanilide (2·5 g; 16 mmole) in anhyd DMSO (30 ml) was kept for 40 days at r.t., subsequently poured into water (150 ml) and kept for 2 days in a refrigerator. The resulting oil which slowly solidified on standing was separated, triturated with EtOH (40 ml) and kept for one day in a refrigerator to yield 1·15 g (22%) of **2a**, m.p. 189–90° from EtOH. (Found: C, 77·16; H, 5·47; N, 12·72. $C_{21}H_{17}N_3O$ (327·39) requires: C, 77·04; H, 5·23; N, 12·84%); IR (KBr): νNH 3450–3100, b, with local maxima at 3380 and 3200; ν(N)–C≡N 2230; Amide I 1675 cm^{-1}. NMR: >C–H δ 4·9 ppm ($CDCl_3$), δ 5·16 ppm (acetone-d_6), δ 5·2 ppm (DMSO-d_6), δ 5·31 ppm (TFA). MS: base peak *m/e* 382 = M-44 with metastable peak at *m/e* 245, calcd 245.

The ethanolic mother liquor was evaporated to dryness, the oily residue was dissolved in benzene, evaporated to dryness again and recrystallized from benzene (30 ml) to yield 1·7 g (39%) of benzilamide containing 1/2 mole of crystal-DMSO, m.p. 141° from benzene. (Found: N, 5·30; S, 6·16. $2C_{14}H_{13}NO_2 + C_2H_6OS$ (532·66) requires: N, 5·26; S, 6·02%).

The mother liquor of the latter product was evaporated to dryness and the oily residue was subjected first to column chromatography (adsorbent: Kieselgel 60, Merck; solvent: benzene–MeOH, 9:1) and then to TLC (adsorbent: Kieselgel $PF_{254+366}$, Merck; thickness of adsorbent layer: 1·5 mm; size of plates 20·20 cm; solvent: benzene–MeOH 6:1; detection: UV light) to yield further 0·12 g (2%) of **2a**, 0·12 g (2%) of **3**, m.p. and lit. m.p.[3] 216–17°, and 0·04 g of **4a**, m.p. and lit. m.p.[3] 289–90°.

(b) **1a** (4·0 g; 16 mmole) and potassium N-cyanoanilide (7·5 g; 48 mmole) reacted under the conditions as above to yield 1·9 g (35%) of **2a**, m.p. 189–90°.

The mother liquor of this product was evaporated to dryness and the oily residue was worked up by column chromatography and subsequent TLC as described under (a) to yield 0·13 g (2·5%) of **2a**, 0·27 g (5%) of **3** and 0·12 g (2·5%) of **4a**.

(c) A soln of **1b**[6] (4·4 g; 14·5 mmole) and potassium N-cyanoanilide (6·8 g; 43·5 mmole) in anhyd DMSO (50 ml) was kept for 4 days at r.t. and subsequently poured into water (100 ml). The mixture was kept for several h in a refrigerator. The crystalline product was separated, thoroughly washed with water and triturated with ether to yield 2·5 g (45%) of **2b**, m.p. 141–142° from benzene–petroleum ether; aqueous acetone. (Found: C, 78·51; H, 6·86; N, 11·15. $C_{25}H_{25}N_3O$ (383·50) requires: C, 78·30; H, 6·57; N, 10·96%). IR (KBr): νNH 3280; ν(N)–C≡N 2225; Amide I 1640 cm^{-1}; NMR ($CDCl_3$): NH δ 6·05 ppm, b; >C–H δ 4·9 ppm; Me_3C δ 1·35 ppm.

The dry residue of the ethereal mother liquor of **2b** was worked up by TLC (adsorbent, thickness of layer and size of plates as above; solvent: cyclohexane–ethyl acetate, 9:1) to yield traces of **4b**, m.p. and lit. m.p.[7]: 153–154°, and **7a**. The latter product is an oil which resisted all attempts of crystallization. Its molecular weight was established by MS.*

(d) A soln of **1c**[10] (4·0 g; 14·5 mmole) and potassium N-cyanoanilide (6·8 g; 43·5 mmole) in anhyd DMSO (25 ml) was kept for 4 months at r.t. and the oily product, obtained after pouring the mixture into water and drying the initially formed crystalline product by evaporation to dryness of its benzene soln, was dissolved in EtOH (20 ml) and kept for a week in a freezer to yield 1·4 g (27%) of **2c**, m.p. 123–124°. (Found: C, 77·38; H, 6·08; N, 12·14. $C_{23}H_{21}N_3O$ (355·44) requires: C, 77·72; H, 5·96; N, 11·82%); IR (KBr): ν(N)–C≡N 2220, Amide I 1645 cm^{-1}; NMR ($CDCl_3$): >C–H δ 5·3 ppm, N-Me δ 3·0 ppm.

The ethanolic mother liquor was evaporated to dryness and the oily residue was extracted by refluxing with two portions of ether (50 ml, each). The oily ethereal extract was worked up by TLC (adsorbent, thickness of layer, size of plates as described above; solvent: benzene–MeOH 9:1) to yield an additional 0·4 g (8%) of **2c**.

(e) A mixture of **1c** (0·5 g; 1·8 mmole), potassium N-cyanoanilide (0·35 g; 2·2 mmole) and dry acetone (10 ml) was refluxed for 40 h. Water (20 ml) was added and the resulting oily ppt was dissolved in EtOH. The resulting soln was dried over $MgSO_4$, evaporated and the residue was worked up by TLC (adsorbent, thickness of layer, size of plates: as above; solvent: cyclohexane–ethyl acetate, 1:1) to yield 0·22 g (34%) of **2c** (R_f 0·4). Several other fractions were also isolated but appear to be mixtures of polymeric products.

Hydrolyses of amides **1a–c**

(a) A soln of **1a** (1·0 g; 4·0 mmole) in anhyd DMSO was poured into water (40 ml). The crystalline ppt (0·83 g; 89%) proved to be identical with benzilamide, m.p. 155–6°, lit. m.p.[14]: 154–5°.

(b) **1b** and **1c**, on similar treatment, furnished the corresponding N-(t-butyl)- and N,N-dimethylamide in 53 and 69% yield, respectively. N-(t-butyl) benzilamide: m.p. 134–135° from gasoline. (Found: C, 76·37; H, 7·36; N, 4·91. $C_{18}H_{21}NO_2$ (283·37) requires: C, 76·30; H, 7·47; N, 4·94%). N,N-dimethylbenzilamide: m.p. 131–132° from gasoline, lit. m.p.[15]: 103°, probably misprinted for 130°. (Found: C, 74·99; H, 6·78; N, 5·72. $C_{16}H_{17}NO_2$ (255·32) requires: C, 75·27; H, 6·71; N, 5·49%).

(c) On treatment of a DMSO solution of **1a** with NaOH aq, an oily product was obtained from which minor amounts of benzilamide could only be isolated.

Degradation of p-(N-*cyanoanilino*)-*diphenylacetamides* **2a–c**

(a) A suspension of **2a** (2 g; 6 mmole) in 20% HCl (80 ml) was refluxed for 6 h. The mixture remained heterogeneous throughout; the undissolved parts turned initially oily but were replaced later by colourless crystals. The latter were separated after the mixture had been chilled, washed with 20% HCl and dried over P_2O_5 *in vacuo* to yield 1·7 g (82%) of **5a**·HCl, colourless crystals which slowly turned green on standing, m.p. 187° (dec.). (Found: N, 4·16; Cl, 9·92. $C_{20}H_{17}NO_2 \cdot HCl$ requires: N, 4·12; Cl, 10·43%).

(b) From **2b** and **2c** 90 and 79%, respectively, of **5a**·HCl, identical according to their m.p.'s and IR spectra with the product obtained as described under (a), were obtained on similar treatment.

(c) **5a**·HCl (0·6 g; 1·8 mmole) was added to NaOH aq (3 ml) soln

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*The authors' thanks are due to Mr. J. Tamás for this determination.

(0·5 g; 12·5 mmole). Only part of **5a** went into soln, part of it formed a red oily supernatant layer. The mixture was evaporated to dryness and the solid residue was subjected to sublimation at 200° (bath temp) and 0·3 torr to yield 76 mg (16·5%) of **5b**, m.p. 53–54° (aqueous MeOH) which, according to the IR spectra and a mixed m.p. determination, proved identical with an authentic sample prepared as described below.

p-*Benzyldiphenylamine* (**5b**)

Compound **5c**[4] (3·5 g; 12·8 mmole) was catalytically reduced in AcOH (250 ml) in the presence of a Pd/C catalyst at an initial pressure of 6 atm. After about 5 h the pressure dropped to 2·8 atm. The catalyst and the solvent were removed. A crystalline crude product was obtained which contained considerable amounts of unchanged starting material. This product was refluxed with gasoline, the mixture was chilled and the insoluble material was filtered off. The oily residue of the gasoline soln was sublimed *in vacuo* at 200° and 0·3 torr to yield 1·5 g of an almost colourless product which was still contaminated with some **5c**. 0·6 g of this product were purified by TLC (adsorbent: Kieselgel G; solvent: benzene–cyclohexane 1:1; elution with ether) to yield 0·39 g **5b** (29% based on the total amount of **5c** introduced), m.p. 57° from aqueous MeOH. (Found: C, 88·01; H, 6·94; N, 5·55. $C_{19}H_{17}N$ (259·35) requires: C, 87·99; H, 6·61; N; 5·40%).

De - t - butylation of 3 - (*t - butyl*) - N(2),5,5 - *triphenylglycocyamidine* (**7a**)

Compound **7a** (0·3 g; 0·8 mmole) was refluxed for 1/2 h with 48% HBr aq (5 ml). The mixture was chilled and the crystalline product was separated and triturated with ethanolic ammonia soln to yield 0·12 g (47%) of **7b**, m.p. and lit.[3] m.p. 331–333°.

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