

Substituted 3-Anilinoindoles and Anilinoacetanilides from the Reaction of Glyoxal with *N*-Alkylanilines: Crystal Structure of 5-Chloro-3-(4-chloro-*N*-methylanilino)-1-methylindole

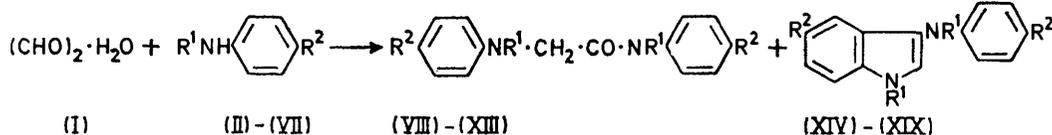
By Paolo Ferruti,* Angelino Ferè, Alberto Bettelli, Marcello Zocchi, Giuseppe Tieghi, and Alberto Albinati, Istituto di Chimica Industriale del Politecnico di Milano, Sezione di Chimica Macromolecolare e Materiali, Piazza Leonardo da Vinci 32, 20133 Milano, Italy

Glyoxal monohydrate reacts with *N*-alkylanilines to give substituted 3-anilinoindoles and anilinoacetanilides in a ratio which, in the absence of catalysts, depends on the amount of water present. Acid catalysts favour formation of indoles. The reaction mechanism is discussed. A single crystal *X*-ray diffraction study of 5-chloro-3-(4-chloro-*N*-methylanilino)-1-methylindole (XVIII) is reported: the crystals are monoclinic, with unit-cell dimensions of $a = 13.96$, $b = 13.34$, $c = 8.96$ Å, and $\beta = 114^\circ 33'$; space-group $P2_1/c$.

GLYOXAL MONOHYDRATE (I) reacts with non-cyclic aliphatic secondary amines to give *N*-substituted aminoacetamides.¹ Some cyclic amines such as morpholine or piperidine, however, behave atypically, yielding 1,1,2,2-tetra-aminoethanes, which in turn easily lose an amino-group on heating, giving 1,1,2-triaminoethylenes.² On the other hand, it was found¹ that the reaction of glyoxal (I) with *N*-methylaniline gave a mixture of *NN'*-dimethylanilinoacetanilide and an indole derivative,

the ratio of indoles and anilinoacetanilides can be altered also by the addition of water. This did not affect the yields of the indoles, but markedly reduced the yields of the anilinoacetanilides. The results for *N*-ethylaniline (II) are given in Table 1.

Kliegman and Barnes³ assigned to the product from *N*-methylaniline the structure, 1-methyl-3-(*N*-methylanilino)indole, apparently only on the basis of a mechanism which they suggested was the most probable and



| | |
|--------------------------|---|
| (III), (VIII), and (XIV) | R ¹ = Et; R ² = H |
| (III), (IX), and (XV) | R ¹ = Pr ⁿ ; R ² = H |
| (IV), (X), and (XVI) | R ¹ = Et; R ² = Me |
| (V), (XI), and (XVII) | R ¹ = Bu ⁿ ; R ² = H |
| (VI), (XII), and (XVIII) | R ¹ = Me; R ² = Cl |
| (VII), (XIII), and (XIX) | R ¹ = Me; R ² = Br |

to which we attributed the structure of 1-methyl-3-(or 2-)(*N*-methylanilino)indole.

Similar results were obtained independently by Kliegman and Barnes,³ who treated glyoxal in water with morpholine, piperidine, and *N*-methylaniline, from the last of which they obtained the indole as the sole product.

The aim of this work was to study the reaction between glyoxal (I) and *N*-alkylanilines, and to confirm unequivocally the structure of the indole derivatives.

When glyoxal (I) was treated with several *N*-alkylanilines, both 3-anilinoindoles and anilinoacetanilides were obtained. The reaction could be made more specific for indoles by the use of acid catalysts. For example, toluene-*p*-sulphonic acid (5% of glyoxal) generally increased the yields of the indoles by a factor of ca. 1.5, while minimizing the yields of the anilinoacetanilides. Strong bases (5% sodium hydroxide) act in the opposite sense, maybe by neutralizing traces of acids present in glyoxal. In the absence of catalysts,

of the n.m.r. spectrum, in which the only proton of the pyrrole group was in the aromatic region.^{1,3} However, alternative mechanisms could be written *a priori*, leading

TABLE 1

Effect of addition of water on the reaction between glyoxal monohydrate (I) (0.1 mol) and *N*-ethylaniline (II) (0.5 mol)

| Water added (mol) | Yield of 1-ethyl-3-(<i>N</i> -ethylanilino)indole (XIV) | Yield of <i>NN'</i> -diethylanilinoacetanilide (VIII) | (XIV) : (VIII) | |
|-------------------|--|---|-------------------|-------------------|
| 0 | 5.7 ^a | 21.6 ^b | 6.15 ^a | 21.8 ^b |
| 0.4 | 5.1 | 19.3 | 5.0 | 17.7 |
| 0.6 | 5.1 | 19.2 | 4.6 | 16.3 |
| 0.8 | 5.0 | 19.0 | 3.3 | 11.7 |
| 1 | 5.2 | 19.7 | 3.5 | 12.4 |
| 2 | 5.3 | 20.0 | 0.7 | 2.5 |

^a Yield in grams. ^b % Yield.

instead to a 2-substituted indole. In this case, deshielding by the two benzene rings could conceivably bring the 3-proton as well into the aromatic region.*

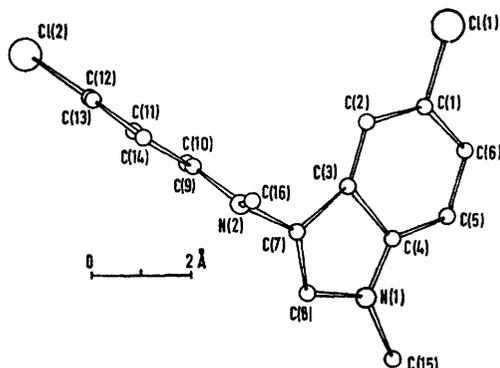
* P. Ferruti, A. L. Segre, and A. Ferè, *J. Chem. Soc. (C)*, 1968, 2721.

³ J. M. Kliegman and R. K. Barnes, *J. Heterocyclic Chem.*, 1970, 7, 1153.

* We thank the referees of our previous paper¹ for having suggested these two points.

¹ P. Ferruti, A. Ferè, L. Zetta, and A. Bettelli, *J. Chem. Soc. (C)*, 1971, 2984.

In order to verify the structure of the indoles, we performed a single-crystal X-ray diffraction study of the chlorophenyl compound (XVIII). As shown in the Figure, the chlorophenyl compound (XVIII) is 5-chloro-1-methyl-3-(4-chloro-*N*-methylanilino)indole. Some bond

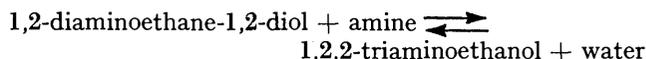


The molecular structure of 5-chloro-3-(4-chloro-*N*-methylanilino)-1-methylindole (XVIII) in the crystal

distances and angles and internal rotation angles are given in Table 2. The plane defined by the indole rings is almost perpendicular to the plane of the aniline substituent. The slight deviation from perpendicularity

1,2,2-triaminoethanols (in turn produced from the 1,2-diaminoethane-1,2-diols by substitution of an amino- for a hydroxy-group) by elimination of a molecule of amine.^{1,4} Therefore, we propose the sequence shown in the Scheme for the reaction between glyoxal (I) and *N*-alkylanilines.

On the basis of this mechanism, the effect of addition of water may be explained as follows. The generation of the anilinoacetanilides is thought to involve the reaction:



This reaction, giving a *gem*-diamino-system, may be reasonably supposed to be easily reversible, and hence to be markedly influenced by the amount of water present. On the other hand, a cyclodehydration leading ultimately to a heteroaromatic molecule, such as that is thought to be involved in the generation of indoles, may be expected to be far less easily reversible, and therefore to be little affected by the presence of water.

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus.

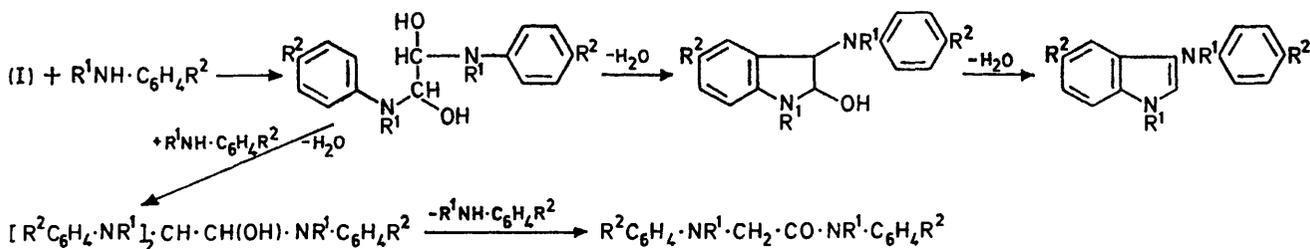
Crystal Data.—C₁₆H₁₄Cl₂N₂, Monoclinic, *a* = 13.96, *b* = 13.34, *c* = 8.96 Å, β = 114° 33'. Space-group *P*2₁/*c*.

TABLE 2

Bond distances and angles and internal rotation angles^a

| Bond distances (Å) | | Bond angles (°) | | Internal rotation angles (°) ^b | |
|--------------------|-------|-----------------|-------|---|-------|
| Cl(1)—C(1) | 1.757 | C(3)—C(7)—C(8) | 107.6 | C(3)—C(7)—N(2)—C(9) | 75.9 |
| Cl(2)—C(12) | 1.746 | C(3)—C(7)—N(2) | 126.8 | C(3)—C(7)—N(2)—C(16) | 88.9 |
| C(7)—N(2) | 1.412 | C(8)—C(7)—N(2) | 125.6 | C(8)—C(7)—N(2)—C(9) | 108.1 |
| C(9)—N(2) | 1.419 | | | C(8)—C(7)—N(2)—C(16) | 87.1 |
| C(15)—N(1) | 1.463 | | | C(7)—N(2)—C(9)—C(10) | 11.3 |
| C(16)—N(2) | 1.449 | | | C(7)—N(2)—C(9)—C(14) | 171.4 |
| | | | | C(10)—C(9)—N(2)—C(16) | 175.8 |
| | | | | C(14)—C(9)—N(2)—C(16) | 6.9 |

^a The average estimated standard deviations σ are as follows: σ(C—Cl) = 0.008 Å, σ(C—N) = 0.009, Å, σ(C—C) = 0.011 Å, σ(N—C—C) = 0.3°, and σ(C—C—C) = 0.4°. ^b The symbol A—B—C—D means the dihedral angle defined by the planes ABC and BCD.



SCHEME

is indicated by the internal rotation angles reported in Table 2.

About the mechanism of the reaction, we agree with Kliegman and Barnes,³ that the indoles are probably formed by cyclodehydration of the corresponding 1,2-diaminoethane-1,2-diols. On the other hand, the anilinoacetanilides probably arise from the appropriate

A single crystal of 5-chloro-3-(4-chloro-*N*-methylanilino)-1-methylindole (XVIII) was mounted on a G.E. X-ray three-circle diffractometer and the diffracted intensities were measured up to a (sin θ)/λ value of 0.59 Å⁻¹, by using a Zr-filtered Mo-*K*_α radiation. The measured intensities were corrected for the Lorentz and polarization factors, but, in view of the small size of the crystal and the low absorption coefficient, no absorption correction was felt to be necessary.

Structure and Refinement.—The structure was solved by

⁴ P. Ferruti, A. Ferè, and L. Zetta, *J. Chem. Soc. (C)*, 1970, 2513.

direct methods with a MULTAN program,⁵ and was refined by least-squares in the block-diagonal approximation. Refinement (based on anisotropic thermal parameters) gave R 0.086 for the 1408 Bragg reflections for which the measured intensities were at least 2.5 times their standard deviations. No attempt was made to locate the H atoms.

NN'-Diethylaminoacetanilide (VIII) and *1-ethyl-3-(N-ethylamino)indole* (XIV).—Glyoxal monohydrate (I) (7.6 g) was stirred at 100° for 2.5 h with *N*-ethylaniline (II) (60.5 g) and dioxan (60 ml). After cooling to room temperature, the mixture was dried (K_2CO_3). Dioxan and the excess of the aniline (II) were then evaporated off *in vacuo* and the residue was distilled at 160–190° and 0.5 mmHg. The distillate was dissolved in ether, the ethereal solution was extracted many times with 3*M*-hydrochloric acid, and the combined acidic extracts were neutralized with alkali and then extracted with ether. The latter ethereal extracts were dried (K_2CO_3) and evaporated *in vacuo*. The residue was then distilled at 162–163° at 0.5 mmHg to give the *anilide* (VIII) (5.6 g, 19.8%) as a clear viscous oil (Found: C, 76.3; H, 7.85; N, 9.9. $C_{18}H_{22}N_2O$ requires C, 76.55; H, 7.85; N, 9.9%).

The former ethereal solution was dried (K_2CO_3), and the solvent was evaporated *in vacuo*. The residue was distilled at 162° and 0.3 mmHg to give the *indole* (XIV) (5.2 g, 19.7%), which crystallized after rubbing under cold methanol, m.p. 52–53° (from methanol) (Found: C, 81.65; H, 7.75; N, 10.35. $C_{18}H_{20}N_2$ requires C, 81.75; H, 7.65; N, 10.6%).

NN'-Di-n-propylanilinoacetanilide (IX) and *1-n-Propyl-3-(N-n-propylanilino)indole* (XV).—The same procedure as before, starting from glyoxal (I) (7.6 g), *N*-n-propylaniline (III) (67.5 g), and dioxan (70 ml) gave the *anilide* (IX) (8.14 g, 26.2%), b.p. 176–180° at 0.35 mmHg (Found: C, 77.05; H, 8.2; N, 9.05. $C_{20}H_{26}N_2O$ requires C, 77.35; H, 8.45; N, 9.0%), and the *indole* (XV) (5.0 g, 17.1%), b.p. 175° at 0.35 mmHg (Found: C, 81.7; H, 8.6; N, 9.3. $C_{20}H_{24}N_2$ requires C, 82.15; H, 8.25; N, 9.6%).

N-Ethyl-(N-ethyl-4-methylanilino)-4-methylacetanilide (X) and *1-Ethyl-3-(N-ethyl-4-methylanilino)-5-methylindole* (XVI).—The same procedure as before, starting from glyoxal (I) (7.6 g), *N*-ethyl-4-methylaniline (IV) (67.5 g), and dioxan (70 ml), gave the *anilide* (X) (9.5 g, 30.6%), b.p. 170–173° at 0.35 mmHg (Found: C, 77.4; H, 8.7; N, 8.9. $C_{20}H_{26}N_2O$ requires C, 77.35; H, 8.45; N, 9.0%), and the *indole* (XVI) (4.85 g, 16.9%), which crystallized after long standing under methanol at 5°, m.p. 45–46° (from methanol), b.p. 170–175° at 0.5 mmHg (Found: C, 81.9; H, 8.5; N, 9.5. $C_{20}H_{24}N_2$ requires C, 82.15; H, 8.25; N, 9.6%).

NN'-Di-n-butylanilinoacetanilide (XI) and *1-n-Butyl-3-(N-n-butylanilino)indole* (XVII).—From glyoxal (I) (7.6 g), *N*-n-butylaniline (V) (75 g), and dioxan (75 ml), the *anilide*

(XI) was prepared (8.7 g, 25.7%), b.p. 179–180° at 0.35 mmHg (Found: C, 78.0; H, 8.75; N, 8.35. $C_{22}H_{30}N_2O$ requires C, 78.05; H, 8.95; N, 8.3%), and the *indole* (XVII) (4.9 g, 15.3%), b.p. 175–177° at 0.35 mmHg (Found: C, 82.6; H, 9.0; N, 8.6. $C_{22}H_{28}N_2$ requires C, 82.45; H, 8.8; N, 8.75%).

4-Chloro-(4-chloro-N-methylanilino)-N-methylacetanilide (XII) and *5-Chloro-3-(4-chloro-N-methylanilino)-4-methylindole* (XVIII).—Glyoxal monohydrate (I) (12.35 g) was stirred at 100° for 3.5 h with 4-chloro-*N*-methylaniline (VI) (137 g) and dioxan (150 ml). After cooling to room temperature, the mixture was dried (K_2CO_3), dioxan and the excess of aniline (VI) were evaporated *in vacuo* and the residue was treated with ether (150 ml) and cooled at 5°. Most of the *anilide* (XII) (10 g) separated at this stage as white crystals, m.p. 113–114° (from methanol) (Found: C, 59.55; H, 4.85; Cl, 21.8; N, 8.55. $C_{16}H_{16}Cl_2N_2O$ requires C, 59.45; H, 5.0; Cl, 21.95; N, 8.65%).

The ethereal solution was evaporated *in vacuo*. Some acetanilide (XII) was shown by t.l.c. (silica; dichloromethane) to be still present in the residue. This was dissolved in dichloromethane and chromatographed [5-cm wide column packed with activity (I) alumina (250 g)]. Elution with dichloromethane (600 ml) gave the *indole* (XVIII) (12.0 g, 24.2%), and further elution with chloroform gave the *anilide* (XII) (4.0 g). The total yield of *anilide* was then 14 g (26.7%). The *indole* (XVIII) was distilled, b.p. 217° at 0.9 mmHg, and the distillate then crystallized by trituration in cold *n*-heptane, m.p. 79–80° (from *n*-heptane) (Found: C, 63.05; H, 4.6; Cl, 23.45; N, 9.2. $C_{16}H_{14}Cl_2N_2$ requires C, 62.95; H, 4.65; Cl, 23.25; N, 9.2%). Crystals of the *indole* (XVIII) suitable for a single crystal X-ray diffraction study were grown by very slow cooling to 30° of a solution saturated at 60 °C of this compound in *n*-heptane.

4-Bromo-(4-bromo-N-methyl)-N-methylacetanilide (XIII) and *5-Bromo-3-(4-bromo-N-methylanilino)-1-methylindole* (XIX).—The same procedure as before [starting from glyoxal (I) (4.9 g), 4-bromo-*N*-methylaniline (VII) (59 g), and dioxan (70 ml)], after eliminating dioxan and the excess of aniline (VII) gave a residue (*ca.* 12 g), which was directly chromatographed [activity (I) alumina] under the previously described conditions. The *anilide* (XIII) (5.5 g, 20.7%), crystallized, m.p. 112–113° (from *n*-heptane) (Found: C, 46.45; H, 4.0; Br, 38.65; N, 6.6%. $C_{16}H_{16}Br_2N_2O$ requires C, 46.65; H, 3.9; Br, 38.8; N, 6.8%), but the *indole* (XIX) (6.5 g, 25.6%) failed to crystallize (Found: C, 48.9; H, 3.7; Br, 40.3; N, 6.95. $C_{16}H_{14}Br_2N_2$ requires C, 48.75; H, 3.6; Br, 40.55; N, 7.1%).

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⁵ G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.