Heterocyclic Nitrogen Compounds. Part I. Some Reactions of 3,6-Dibenzylidene-2,5-dioxopiperazines

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2,5-Dioxopiperazine did not react with carbonyl reagents or condense with ketones. It condensed with aldehydes to give 3,6-dibenzylidene-derivatives. The latter reacted with Grignard reagents to give 1,4-addition on one side only.

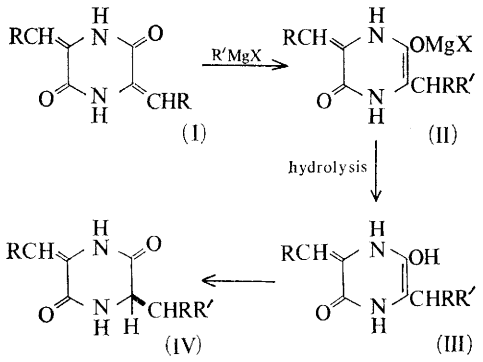
2,5-DIOXOPIPERAZINES derive their importance from the fact that they are amino-acid anhydrides, and from the pharmacodynamic activity of many of their derivatives.

Their carbonyl groups were shown not to react with phenylhydrazine or hydroxylamine.[1] They also, we found, did not react with semicarbazide. The hydrogen atoms attached to the nitrogen did not react with chloroacetic acid to give the acetic acid derivatives, and they did not condense with aromatic or aliphatic ketones. However, they reacted with aromatic aldehydes to give 3,6-dibenzylidene-derivatives [2] which reacted with bromine in hot glacial acetic acid to give the dibromo-derivative. When the dibromo-derivative was oxidised with aqueous alkaline potassium permanganate, it gave benzoic acid. Thus the bromination was not in the benzene rings. The absence of the bromine atoms in the benzene nuclei was also shown by the presence of two strong infrared bands at 700 and 760 cm.$^{-1}$ characteristic of the stretching frequency of 5 adjacent aromatic hydrogen atoms.[3] The bromine atoms were stable to hydrolysis when boiled with 10% aqueous sodium hydroxide, thus eliminating the possibility of a hydrobromide or bromine attached to the nitrogen. The presence in the i.r. spectrum of a band at 3448 cm.$^{-1}$, characteristic of the NH of cyclic amides,[3] in the compound before and after bromination confirms the latter fact. A comparison experiment was run with succinimide before and after bromination, where the strong broad band at 3225—3125 cm.$^{-1}$ characteristic of the NH in succinimide is not shown in *N*-bromosuccinimide. So the bromine atoms in the dioxopiperazine must arise by substitution of the hydrogen atoms of the two vinyl groups and not the hydrogens on the nitrogen atoms as has been reported by Goldschmidt *et al.*[4]. The dibromo-compound when reduced by zinc and hydrochloric acid afforded the dibenzyl derivative which is further evidence that the bromine was substituted on the aliphatic part.

Reduction of 3,6-dibenzylidene-2,5-dioxopiperazine with zinc and hydrochloric acid in acetic acid or by catalytic hydrogenation in presence of Raney nickel gave 3,6-dibenzyl-2,5-dioxopiperazines. The i.r. spectrum of this compound showed a strong band at 1695 cm.$^{-1}$ characteristic of the carbonyl group, and no bands characteristic of OH or C=C.

3,6-Dibenzylidene-2,5-dioxopiperazine did not react with diazomethane, thus eliminating any possibility of enolisation, and so it exists in the keto-form. This was also shown by the absence of any OH band in the 3500 cm.$^{-1}$ region.

Kapfhammer and Matthes [5] had shown that sarcosine anhydride reacted with ethylmagnesium bromide to give hexa-alkylpiperazine, while with phenylmagnesium bromide it underwent fission to give methylaminoacetophenone and sarcosylaminoacetophenone. Proline anhydride with phenylmagnesium bromide also underwent fission to give pyrrolidinyldiphenylmethyl *N*-pyrrolidinyl phenyl ketone. 3,6-Diarylalkylidene-2,5-dioxopiperazine, we found, did not undergo fission, and did not even react on both carbonyl groups. The reaction was 1,4-addition on one side only. This proposed reaction scheme was supported by trapping structure (III) by methylation of the magnesium compound (II) with dimethyl sulphate, when the methyl ether of (III) was separated.



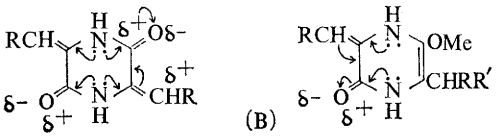
The i.r. spectrum of 3-(p-*tolylphenylmethyl*)-6-(4'-*methylbenzylidene*)-2,5-*dioxopiperazine* gave maxima at 3448, 3175, 1695, 1639, 3030, 1515, and 1262 cm.$^{-1}$ which are consistent with the structure (IV) proposed.[3]

Although an excess of the Grignard reagent was used, the reaction occurred on one side only. The non-reactivity on the other side could not be due to the insolubility of compound (II) since the ether of compound (III) after its isolation, when treated with

[1] A. Spiridonova, *J. Gen. Chem.* (*U.S.S.R.*), 1936, **6**, 137.
[2] T. Sasaki, *Ber.*, 1921, **54**, 163.
[3] L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules,' Methuen, London, 1964.
[4] S. Goldschmidt, E. Wiberg, F. Nagel, and K. Martin, *Annalen*, 1927, **456**, 1.
[5] J. Kapfhammer and A. Matthes, *Z. physiol. Chem.*, 1933, **223**, 43.

phenylmagnesium bromide, gave back the starting ether (III). It cannot be due to enolisation of the second carbonyl as compound (IV), when treated with phenylmagnesium bromide and benzoylated or methylated, was isolated unchanged.

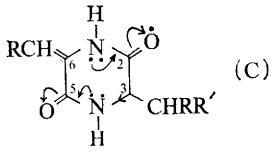
Also, it was found that 3,6-di-(2′-, 3′-, and 4′-chlorobenzylidene)-2,5-dioxopiperazines did not react at all with phenylmagnesium bromide. So the non-reactivity cannot be due to the electron-donating character of the phenyl, 4-methyl-, or 4-methoxy-phenyl groups which



(A) (B)

R = Ph, C_6H_4·Me-*p*, C_6H_4·OMe-*p*

may destroy the positive charge on the *exo*-olefinic carbon atom. It appears that the lone electron pairs on the two nitrogen atoms are delocalised to reduce the positive charge on the carbonyl carbon and the *exo*-olefinic carbons. The presence of electron-donating groups favours the Grignard reaction by assisting electron-delocalisation of the initial double bonds to give the polarised structure which could not be completely weakened by the partition of the lone pairs of electrons on the two nitrogens in the two directions as shown in structure (A). When one side is attacked as in the methyl ether of compound (III) the lone pairs on the nitrogen will intensively neutralise the positive charges on the other carbonyl group and prevent the polarisation of the olefinic bond so that no second nucleophilic attack is possible. The resulting addition



(C)

product (IV) is highly deactivated towards the Grignard reagent since the electron pair on the nitrogen which is attached to a saturated chain (C) highly delocalises towards C-5 and so deactivates it completely, while the lone pair of N-1 is delocalised towards C-2 thus preventing this carbonyl from any reaction. The non-reactivity of the chlorophenyl derivatives may also be explained by the same delocalisation mechanism. The carbonyl groups and the chlorine atoms, both electron-attracting, may lead to the formation of two adjacent positive charges that result in suppression of the polarisation of the carbonyl groups and thus lead to deactivation; this deactivation is enhanced by the presence of the two nitrogen atoms adjacent to the carbonyl carbons.

The i.r. spectra were run in KBr using an Infracord 137 spectrophotometer.

EXPERIMENTAL

Condensations of 2,5-Dioxopiperazine. (a) *With* p-*tolualdehyde.* A mixture of acetic anhydride (13 g., 0·13 mole), anhydrous sodium acetate (6·6 g., 0·08 mole), 2,5-dioxopiperazine (2·28 g., 0·02 mole), and *p*-tolualdehyde (4·8 g., 0·04 mole) was heated for 3 hr. at 130—140° in an oil-bath until a solid cake was formed. The mixture was washed with hot water, filtered, and washed with small amounts of ether to dissolve any resins. Crystallised from acetic acid it afforded 3,6-*di*-(4′-*methylbenzylidene*)-2,5-*dioxopiperazine* (2·0 g.) as a yellow crystalline powder, m.p. 284° (Found: C, 75·9; H, 6·1; N, 8·3. $C_{20}H_{18}N_2O_2$ requires C, 75·5; H, 5·7; N, 8·8%).

(b) *With* p-*anisaldehyde.* From a reaction as before using 5·5 g. of *p*-methoxybenzaldehyde (0·04 mole) and 12 hr. reflux, a solid dark cake was obtained. The mixture was washed with water, filtered, and washed with ethanol until it aquired a golden yellow colour. Crystallisation from glacial acetic acid gave 3,6-*di*-(4′-*methoxybenzylidene*)-2,5-*dioxopiperazine* (3·5 g.), m.p. 318°; it gave an orange brown colour with conc. sulphuric acid (Found: C, 68·1; H, 5·4; N, 8·0. $C_{20}H_{18}N_2O_2$ requires C, 68·1; H, 5·1; N, 8·0%).

(c) *With* p-*chlorobenzaldehyde.* The same reaction was repeated using *p*-chlorobenzaldehyde (5·65 g., 0·04 mole) and afforded, after the usual treatment and washing with water and then ethanol, shiny yellow crystals (2·3 g.), insoluble in common solvents. It was purified by boiling with the common solvents. 3,6-*Di*-(4′-*chlorobenzylidene*)-2,5-*dioxopiperazine* melted above 360° (Found: C, 60·3; H, 3·6; N, 8·1. $C_{18}H_{12}Cl_2N_2O_2$ requires C, 60·2; H, 3·3; N, 7·8%).

(d) *With* m-*chlorobenzaldehyde.* In a reaction as above, *m*-chlorobenzaldehyde (5·65 g., 0·04 mole) gave 3,6-*di*-(4′-*chlorobenzylidene*)-2,5-*dioxopiperazine* (1·5 g.), shiny yellow crystals from acetic acid, m.p. 280°; it gave a lemon-yellow colour with conc. sulphuric acid (Found: C, 59·6; H, 3·7; N, 8·0%).

This reaction was repeated with acetone and with benzophenone but afforded the starting substances.

Treatment of 3,6-*Di*-(4′-*methoxybenzylidene*)-2,5-*Dioxopiperazine with Hydrochloric Acid.*—The substance dissolved in glacial acetic acid with dilute hydrochloric acid was refluxed for 4 hr. After the usual treatment the starting dioxopiperazine was isolated unchanged, m.p. and mixed m.p. 318°.

Reduction of 3,6-*Dibenzylidene*-2,5-*dioxopiperazine.*—(a) *With zinc and hydrochloric acid.* 3,6-Dibenzylidene-2,5-dioxopiperazine (0·99 g., 0·0034 mole), glacial acetic acid (80 c.c.), concentrated hydrochloric acid (5 c.c.), and zinc dust (7 g.) were refluxed for 7 hr., then filtered while hot and diluted with water. The solid 3,6-*dibenzyl*-2,5-*dioxopiperazine* (0·5 g.) crystallised from glacial acetic acid as colourless needles, m.p. 280°, and gave a yellow colour with conc. H_2SO_4 (Found: C, 72·8; H, 6·0; N, 9·7. $C_{18}H_{18}N_2O_2$ requires C, 73·1; H, 5·8; N, 9·5%).

(b) *By catalytic hydrogenation.* A solution of 3,6-dibenzylidene-2,5-dioxopiperazine (0·52 g., 0·0018 mole) in glacial acetic acid (50 c.c.) with platinum catalyst (0·25 g.) was shaken under hydrogen until 80 c.c. of hydrogen (0·0035 mole) had been absorbed. The solution was filtered and diluted with water and ice. The solid formed crystallised from glacial acetic acid, m.p. and mixed m.p. 280° (Found: C, 73·4; H, 5·7; N, 9·5. Calc. for $C_{18}H_{18}N_2O_2$: C, 73·1; H, 5·8; N, 9·5%).

Bromination of 3,6-*Dibenzylidene*-2,5-*dioxopiperazine*.—A solution of bromine (6·4 g., 0·04 mole) in acetic acid was added dropwise to a solution of 3,6-dibenzylidene-2,5-dioxopiperazine (2·9 g., 0·01 mole) in glacial acetic acid (100 c.c.) while stirring. The solution was then heated on a water-bath for 3 hr. The precipitate (4·5 g.) crystallized from nitrobenzene to give 3,6-*di*-(α-*bromobenzylidene*)-2,5-*dioxopiperazine*, m.p. 321°; it gave a lemon-yellow colour with conc. H_2SO_4 (Found: C, 48·5; H, 2·9; Br, 35·3; N, 6·2. $C_{18}H_{12}Br_2N_2O_2$ requires C, 48·2; H, 2·7; Br, 35·7; N, 6·5%).

An attempt to hydrolyse the above product with a 10% aqueous solution of sodium hydroxide under reflux gave back the starting dibromo-compound, m.p. and mixed m.p. 321°.

Oxidation of 3,6-*Di*-(α-*bromobenzylidene*)-2,5-*dioxopiperazine*.—The dibromo-compound (1·0 g.) was suspended in 5% aqueous sodium hydroxide solution (50 c.c.), stirred, and heated to boiling. A saturated potassium permanganate solution was added until no further decolouration took place. The reaction mixture was then cooled, acidified with hydrochloric acid, and the crystalline solid isolated by filtration. Recrystallised from hot water, it had m.p. and mixed m.p. with an authentic sample of benzoic acid 121°.

Reduction of the Dibromo-compound.—Zinc dust (7·0 g.) was added portionwise to a mixture of the dibromo-product (0·9 g.), glacial acetic acid (100 c.c.), and hydrochloric acid (10 c.c.). The mixture was heated for 7 hr. on a water-bath, filtered, and diluted with water. On standing and cooling, 3,6-dibenzyl-2,5-dioxopiperazine crystallised out. Recrystallised from glacial acetic it had m.p. and mixed m.p. 280°, and gave a yellow colour with conc. H_2SO_4.

Bromination of 3,6-*Di*-(4′-*methoxybenzylidene*)-2,6-*dioxopiperazine*.—From a reaction as above in glacial acetic acid, the addition of bromine gave 3,6-*di*-(α-*bromo*-4′-*methoxybenzylidene*)-2,5-*dioxopiperazine*, m.p. 277° (from glacial acetic acid); it gave a yellow colour with conc. H_2SO_4 (Found: N, 5·7. $C_{20}H_{16}Br_2N_2O_2$ requires N, 5·5%).

Action of Phenylmagnesium Bromide on 3,6-*Dibenzylidene*-2,5-*dioxopiperazine*.—To a solution of phenylmagnesium bromide [prepared from bromobenzene (4·4 g., 0·03 mole)] in dry ether, a solution of 3,6-dibenzylidene-2,5-dioxopiperazine (1·5 g., 0·005 mole) in dry benzene (30 c.c.) was added. The mixture, left overnight, was refluxed for 4 hr., and then cooled. It was decomposed with water acidified with hydrochloric acid. The combined organic layer and the ethereal extract of the aqueous layer were washed with water, dried (Na_2SO_4), and filtered. The oily residue that remained after the evaporation of the solvents solidified (0·7 g.) under ethanol and crystallised therefrom. 3-*Diphenylmethyl*-6-*benzylidene*-2,5-*dioxopiperazine* melted at 260° and gave a yellow-brown colour with conc. H_2SO_4 (Found: C, 78·1; H, 5·6; N, 7·2. $C_{24}H_{20}N_2O_2$ requires C, 78·4; H, 5·5; N, 7·6%).

Methylation of the Above Magnesium Complex.—The above reaction was repeated; dimethyl sulphate (6 g.) was added to the magnesium complex and the mixture was refluxed for a further 2 hr., cooled, decomposed with iced water, and acidified with hydrochloric acid. The organic and the ethereal extract of the aqueous layer were united and washed with sodium hydroxide (5% solution) and then with water until neutral, dried (Na_2SO_4), and filtered. On evaporation of the solvents, an oil remained that solidified (0·5 g.) under ethanol and crystallised therefrom. 3-*Diphenylmethyl*-6-*benzylidene*-2-*methoxy*-5-*oxo*-2,3-*dehydropiperazine* melted at 275° and gave a yellow-brown colour with conc. H_2SO_4 (Found: C, 74·7; H, 6·0; N, 7·0. $C_{25}H_{22}N_2O_2,H_2O$ requires C, 75·0; H, 6·0; N, 7·0%).

Action of Phenyl-lithium on 3,6-*Dibenzylidene*-2,5-*dioxopiperazine*.—A cold solution of 3,6-dibenzylidene-2,5-dioxopiperazine (1·5 g., 0·005 mole) in dry benzene (30 c.c.) was added to a solution of phenyl-lithium [prepared from bromobenzene (4·4 g., 0·03 mole)]. The reaction mixture was left overnight, refluxed for 4 hr., and then decomposed with cold water acidified with hydrochloric acid. The combined organic layer and the ethereal extract of the aqueous layer were washed with water, dried (Na_2SO_4), and filtered. The solvents were evaporated. The residual oil solidified (0·4 g.) under ethanol and cooling. Recrystallised from ethanol, it melted at 260° and gave no depression in m.p. when mixed with the same compound obtained from the magnesium reaction above.

Action of Ethylmagnesium Bromide on 3,6-*Dibenzylidene*-2,5-*dioxopiperazine*.—To a cold ethereal solution of ethylmagnesium bromide [prepared from ethyl bromide (4·3 g., 0·04 mole)], a solution of 3,6-dibenzylidene-2,5-dioxopiperazine (1·5 g., 0·005 mole) in dry benzene was added. The reaction mixture was left overnight, then refluxed for 4 hr. The magnesium complex was decomposed with a mixture of crushed ice and dilute hydrochloric acid. The ethereal layer was combined with the ethereal extract of the aqueous layer, and they were washed, dried (Na_2SO_4), and filtered. When the solvents were evaporated, the residual oil solidified (1·1 g.) under ethanol and crystallised therefrom. 3-α-*Ethylbenzyl*-6-*benzylidene*-2,5-*dioxopiperazine* melted at 275° (Found: N, 9·5. $C_{20}H_{20}NO_2$ requires N, 8·8%).

Action of Phenylmagnesium Bromide on 3,6-*Di*-(4′-*methylbenzylidene*)-2,5-*dioxopiperazine*.—To a solution of phenylmagnesium bromide [from bromobenzene (1·1 g., 0·01 mole)], a solution of 3,6-di-(4′-methylbenzylidene)-2,5-dioxopiperazine (0·4 g., 0·0013 mole) in dry benzene (30 c.c.) was added. The mixture was treated as before. The residual oil that remained after the evaporation of the solvents crystallised (0·3 g.) under ethanol and cooling and recrystallised therefrom; 3-(*phenyl*-4′-*methylphenylmethyl*)-6-(4″-*methylbenzylidene*)-2,5-*dioxopiperazine* had m.p. 275° (Found: C, 75·1; H, 6·0; N, 7·1. $C_{26}H_{24}N_2O_2,H_2O$ requires C, 75·3; H, 6·3; N, 6·8%).

Action of Ethylmagnesium Bromide on 3,6-*Di*-(4′-*methylbenzylidene*)-2,5-*dioxopiperazine*.—A solution of 3,6-di-(4-methylbenzylidene)-2,5-dioxopiperazine (0·5 g., 0·0016 mole) in dry benzene (30 c.c.) was added to a solution of ethylmagnesium bromide (from 1·3 g. of ethyl bromide, 0·013 mole) in dry ether. The mixture was treated as above and the residual oil solidified (0·3 g.) under ethanol and crystallised therefrom, m.p. 240° (Found: C, 75·5; H, 6·5; N, 7·1. $C_{22}H_{24}N_2O_2$ requires C, 75·8; H, 6·9; N, 8·0%).

Action of Phenylmagnesium Bromide on 3,6-*Di*-(4′-*methoxybenzylidene*)-2,5-*dioxopiperazine*.—A solution of 3,6-di-(4′-methoxybenzylidene)-2,5-dioxopiperazine (1·8 g., 0·005 mole) in benzene (30 c.c.) and phenylmagnesium bromide (from 6·9 g., 0·04 mole of bromobenzene) in a reaction as above gave an oil that solidified (2·0 g.) under aqueous ethanol and crystallised therefrom; 3-(4′-*methoxydiphenylmethyl*)-6-(4″-*methoxybenzylidene*)-2,5-*dioxopiperazine* melted at 250° (Found: C, 67·3; H, 5·7; N, 6·8. $C_{26}H_{22}N_2O_2,2H_2O$ requires C, 67·5; H, 5·8; N, 6·1%).

Action of Ethylmagnesium Bromide on 3,6-*Di*-(4′-*methoxybenzylidene*)-2,5-*dioxopiperazine*.—From a reaction as above using ethylmagnesium bromide (from 2·5 g., 0·025 mole, of ethyl bromide) in ether and 3,6-di(methoxybenzylidene)-2,5-dioxopiperazine (1 g., 0·002 mole) in dry benzene 3-(α-*ethyl*-4′-*methoxyphenylmethyl*)-6-(4″-*methoxybenzylidene*)-2,5-*dioxopiperazine* (0·6 g.) was obtained that cyrstallised from ethanol, m.p. 266° (Found: N, 8·0. $C_{22}H_{24}N_2O_4$ requires N, 7·4%).

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