

PATENT SPECIFICATION

NO DRAWINGS

1,122,962

1,122,962



Date of Application and filing Complete Specification: 11 Jan., 1967.
No. 1579/67.

Application made in United States of America (No. 521,539) on 19 Jan., 1966.
Complete Specification Published: 7 Aug., 1968.

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Index at acceptance:—C2 C(1F2A1, 1F2C6, 1F2D2, 1G5B, 1G6B5, 1J1A4, 1J1B, 1J1C2)

Int. Cl.:—C 07 c 97/10, C 07 d 53/06

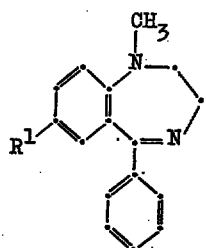
COMPLETE SPECIFICATION

Benzophenone Derivatives and the Conversion thereof into
Benzdiaz[1,4]Epines

We, F. HOFFMANN-LA ROCHE & Co.,
AKTIENGESSELLSCHAFT, a Swiss Company of
124—184 Grenzacherstrasse, Basle, Switzer-
land, do hereby declare the invention, for
which we pray that a patent may be granted
to us, and the method by which it is to be per-
formed, to be particularly described in and
by the following statement:—

The present invention relates to benzo-
phenone derivatives and the conversion thereof
into benzdiaz[1,4]epines. More particularly,
the invention is concerned with a process for
the manufacture of certain 7 - halo - 1 -
methyl - 5 - phenyl - 2,3 - dihydro - 1H -
benzdiaz[1,4]epines from certain novel benzo-
phenone derivatives, with the preparation of
said derivatives and with said derivatives *per se*.

The benzdiaz[1,4]epines obtained by carry-
ing out the process of this invention are com-
pounds of the general formula



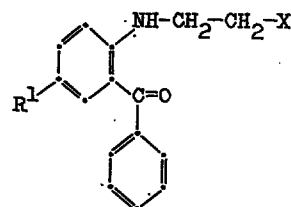
(I)

wherein R¹ represents a chlorine or bromine
atom (preferably a chlorine atom). These com-
pounds are claimed *per se* in the specification
of our Letters Patent No. 1,017,276.

Compounds of formula I have heretofore
been obtained by methylating the appropriate
1 - unsubstituted - 7 halo - 5 - phenyl - 2,3 -
dihydro - 1H - benzdiaz[1,4]epine. This pro-
cedure involves the formation of a sodio
derivative of the said 1-unsubstituted com-
pound and reaction of the sodio derivative
[Price 4s. 6d.]

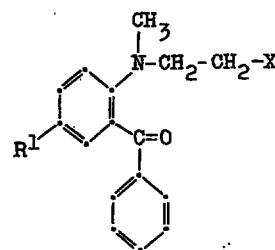
with a methylating agent such as dimethyl
sulphate or methyl iodide. It has been found,
however, that the desired 1-substituted com-
pounds of formula I are not obtained accord-
ing to this procedure in yields of an order
which would make the procedure very attrac-
tive where large quantities are needed.

It has now been found in accordance with
the present invention that the compounds of
formula I hereinbefore can be readily manu-
factured in high yields and in good quality
(particularly on a large scale) by treating a
2 - amino - benzophenone derivative of the
general formula



(II)

wherein R¹ has the significance given earlier
and X stands for a chlorine, bromine or iodine
atom, with a methylating agent and reacting
the resulting 2 - methylamino - benzophenone
derivative of the general formula



(III)

wherein R¹ and X have the significance given
earlier, with ammonia.

SEE ERRATA SLIP ATTACHED

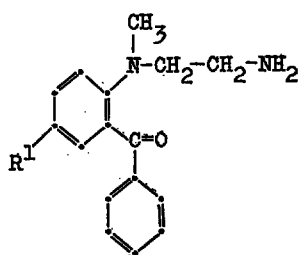
Accordingly, the process for the manufacture of the compounds of formula I hereinbefore comprises treating a 2 - amino - benzophenone derivative of formula II hereinbefore with a methylating agent and reacting the resulting 2 - methylamino - benzophenone derivative of formula III hereinbefore with ammonia.

The preferred 2 - amino - benzophenone derivatives of formula II used as starting materials in the present process are those in which R^1 represents a chlorine atom. Further, the preferred methylating agent is a system comprising formaldehyde (or a substance such as paraformaldehyde which yields formaldehyde under the conditions of the treatment) and formic acid.

Temperature and pressure are not critical features of the treatment of a 2 - amino - benzophenone derivative of formula II with the methylating agent or the subsequent reaction of the 2 - methylamino - benzophenone derivative of formula III with ammonia. Accordingly, the treatment and reaction can be carried out at room temperature or at temperatures above or below room temperature. However, the treatment and reaction are advantageously carried out with the application of heat (i.e. at elevated temperatures).

The reaction of a 2 - methylamino - benzophenone derivative of formula III with ammonia brings about ammonolysis and ring-closure to the desired compound of formula I. Suitably, the reaction with ammonia is carried out in the presence of an inert organic solvent such as an alkanol containing from one to seven carbon atoms (e.g. ethanol) or an ether (e.g. dioxan or tetrahydro-furan).

The reaction of a 2 - methylamino - benzophenone derivative of formula III hereinbefore with ammonia proceeds through an intermediate of the general formula



(IV)

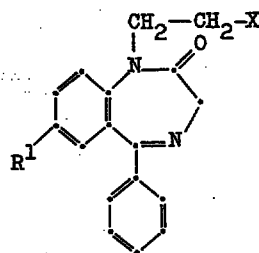
wherein R^1 has the significance given earlier. These intermediates are not isolated but are directly converted to the desired compounds of formula I under the conditions of the reaction.

As will be evident from the foregoing, the present process is eminently well-suited for handling large quantities of starting materials and products. Furthermore, the desired com-

pounds of formula I are obtained in good yields and of a high quality without being contaminated by an inconvenient amount of impurities. Wearisome and expensive purification steps are thus saved.

The 2 - amino - benzophenone derivatives of formula II hereinbefore can be prepared by a variety of methods.

One such method, which forms a further and initial step of the process of this invention, comprises hydrolysing a benzdiaz[1,4]epinone-(2) of the general formula

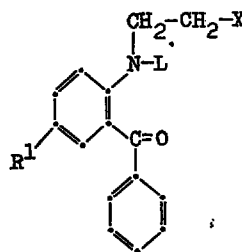


(V)

wherein R^1 and X have the significance given earlier. The hydrolysis is carried out using any suitable hydrolysing agent; for example, mineral acids such as hydrochloric acid. Preferably, an alkanol containing from one to seven carbon atoms such as ethanol is present during the hydrolysis. Thus, the hydrolysis is preferably carried out using an alkanolic solution of a mineral acid (e.g. ethanolic hydrochloric acid).

The benzdiaz[1,4]epinone-(2)'s of formula V hereinbefore are claimed *per se* in the specification of our Letters Patent No. 1,050,401.

Another such method, which also forms a further and initial step of the process of this invention, comprises heating a compound of the general formula

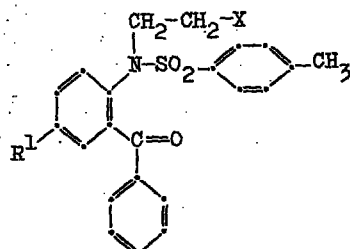


(VI)

wherein R^1 and X have the significance given earlier and L represents a nitrogen-protecting leaving group, in the presence of a proton-donating acid agent (e.g. sulphuric acid).

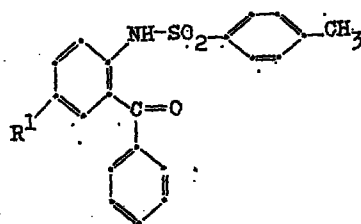
In this last-mentioned method it is pre-

ferred to use a compound of formula VI in which L represents a tosyl group; that is to say, a compound of the general formula



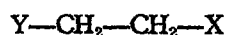
(VIa)

- 5 wherein R¹ and X have the significance given earlier. The compounds of formula VIa can be obtained by reacting a tosylamino-benzophenone of the general formula



(VII)

- 10 wherein R¹ has the significance given earlier, with a 1,2 - dihalo - ethane of the general formula



- 15 wherein X has the significance given earlier and Y stands for a chlorine, bromine or iodine atom (e.g. 1,2 - dichloro - ethane, 1,2 - di-bromo - ethane or 1 - chloro - 2 - bromo - ethane). The reaction is preferably carried out by converting the tosylamino-benzophenone of formula VII into its N-sodio derivative (e.g. using sodium hydride or sodium methoxide) prior to reaction with the 1,2 - dihalo - ethane.

- 20 While the last-mentioned method is described in detail with reference to the tosyl group as the leaving group in compounds of formula VI, it will, of course, be understood that any equivalent leaving group such as another arylsulphonyl group (e.g. benzenesulphonyl) or a carboxylic acyl group (e.g. acetyl) can be present in the compounds of formula VI in place of the tosyl group. Preferably, however, the leaving group is a carboxylic acyl group, the benzenesulphonyl group or a benzenesulphonyl group carrying a substituent which is inert under the reaction conditions employed. However, all that is

required of the leaving group is that it functions efficaciously in this method; that is to say, that it protects the aniline nitrogen atom during the alkylation step and, further, that it can be readily removed as described earlier.

The 2 - amino - benzophenone derivatives of formula II and the 2 - methylamino - benzophenone derivatives of formula III are novel and it will be appreciated that they also form part of this invention.

The following Examples illustrate the present invention:

EXAMPLE 1

A) The preparation of the starting material:

(i) A solution of 10 g (30mmol) of 7 - chloro - 1 - (2 - chloro - ethyl) - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz[1,4]epinone - (2) in 100 ml of ethanol and 100 ml of 3-N hydrochloric acid was heated at reflux with stirring over a period of 19 hours. The resulting mixture was poured into an excess of iced sodium hydroxide and extracted with methylene chloride. The extract was washed with water and the methylene chloride was removed by evaporation *in vacuo* to give a yellow oil. Chromatography of this oil over an alumina (WOELM neutral, activity 1) column and passing petroleum ether (boiling range 40°—60°C) through the column gave 5 - chloro - 2 - (2 - chloro - ethylamino) - benzo - phenone in the petroleum ether eluate. After crystallization and recrystallization from (methylene chloride)/hexane 5 - chloro - 2 - (2 - chloro - ethylamino) - benzophenone was obtained as yellow prisms of melting point 88°—90°C.

(ii) A mixture of 82 g (0.2 mol) of the sodium salt of 2 - paratoluenesulphonamido - 5 - chloro - benzophenone and 144 g (0.2 mol) of 1 - bromo - 2 - chloro - ethane in 500 ml of N,N - dimethyl - formamide was stirred overnight at 70°—75°C. The resulting mixture was poured into 1 litre of water and extracted with three 200 ml portions of methylene chloride and the combined extracts were washed with 3-N sodium hydroxide and then with water, and evaporated *in vacuo*. The glassy residue thus obtained was allowed to stand at room temperature for about 30 days. Subsequent recrystallization from a mixture of ether and petroleum ether (boiling range 40°—60°C) gave 5 - chloro - 2 - [N - (2 - chloro - ethyl) - paratoluenesulphonamido] - benzophenone as colourless waxy prisms melting at 97°—101°C.

200 ml of concentrated sulphuric acid were carefully added to 0.2 ml of 5 - chloro - 2 - [N - (2 - chloro - ethyl) - paratoluene - sulphonamido] - benzophenone and the resulting mixture was stirred for 0.5 hour. 30 ml of water were then carefully added and the mixture was stirred at 100°C for 40 minutes,

cooled to room temperature and allowed to stand overnight. The mixture was subsequently poured over 1 kg of ice and the solution obtained neutralised with potassium hydroxide.

- 5 The resulting potassium sulphate was removed by filtration, the precipitate washed with methylene chloride and the filtrate extracted several times with methylene chloride. The combined methylene chloride washings and
10 extracts were washed several times with water and evaporated *in vacuo* to give 5 - chloro - 2 - (2 - chloro - ethylamino) - benzophenone as a yellow oil which crystallized on standing; melting point = 85°—90°C.

15 B) The process:

- A solution of 27.6 g (94 mmol) of 5 - chloro - 2 - (2 - chloro - ethylamino) - benzophenone in 200 ml of 98—100% formic acid was treated with 25 g of paraformaldehyde. The resulting mixture was stirred at 61°C for 18 hours, then the formic acid was removed by evaporation *in vacuo* at 55°C. The residue was treated with 200 ml of iced 3-N sodium hydroxide and the resulting mixture
20 was extracted with methylene chloride. Removal of the methylene chloride from the extract by evaporation left an orange oil which was dissolved in 500 ml of ether and 100 ml of benzene. The mixture thus formed was
30 extracted with three 125 ml portions of cold 5-N hydrochloric acid. The combined acid extracts were washed with benzene, neutralised with potassium hydroxide and extracted with methylene chloride. The methylene chloride
35 extract was washed with water, combined with benzene and evaporated *in vacuo* to give 5 - chloro - 2 - [N - (2 - chloro - ethyl) - N - methyl - amino] - benzophenone as an orange oil of boiling point 175°—178°C/0.2 mm.

- 40 A mixture of 10 g (32.5 mmol) of 5 - chloro - 2 - [N - (2 - chloro - ethyl) - N - methyl - amino] - benzophenone, 10 g (67 mmol) of sodium iodide and an excess of ammonia in 25 ml of ethanol was placed in a sealed container, heated to 85°C and shaken for 10
45 hours. The resulting mixture was evaporated *in vacuo* to give a red gum which was partitioned between 1-N sodium hydroxide and benzene. The benzene layer was extracted with three 50 ml portions of 1-N hydrochloric acid. The combined acidic extracts were washed
50 with benzene and made basic with sodium hydroxide. Extraction with benzene and removal of the solvent from the extract by evaporation *in vacuo* gave a crystalline residue of 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz[1,4] epine of melting point 100°—103°C.

EXAMPLE 2

- 60 A) The preparation of the starting material:

- A mixture of 41 g (0.1 mol) of the sodium salt of 2 - *paratoluenesulphonamido* - 5 - chloro - benzophenone, 94 g (0.5 mol) of 1,2 - dibromo - ethane and 350 ml of N,N - di -
65 methyl - formamide was stirred overnight at

75°C. The resulting mixture was poured into 1 litre of water and extracted with three 200 ml portions of methylene chloride. The combined extracts were washed with 10-N sodium hydroxide and then with water, and evaporated
70 *in vacuo*. The glassy residue was crystallized and recrystallized from ether/hexane to give 5 - chloro - 2 - [N - (2 - bromo - ethyl) - *paratoluenesulphonamido*] - benzophenone as colourless prisms of melting point 114°—116°C.

0.1 mol of 5 - chloro - 2 - [N - (2 - bromo - ethyl) - *paratoluenesulphonamido*] - benzophenone were added with stirring to 150 ml of concentrated sulphuric acid, 50 ml of water were then carefully added and the mixture was stirred at reflux for 0.5 hour and subsequently poured into iced potassium hydroxide. The precipitate which formed was removed by filtration. Air drying of the precipitate gave
80 2 - (2 - bromo - ethylamino) - 5 - chloro - benzophenone as yellow needles of melting point 90°—95°C. Recrystallization from ethanol/water gave yellow needles melting at 92°—94°C.

B) The process:

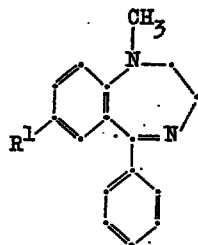
A solution of 21 g (62 mmol) of 2 - (2 - bromo - ethylamino) - 5 - chloro - benzophenone was stirred into 200 ml of 98—100% formic acid. 20 g of paraformaldehyde were then added and the mixture turned dark red. The mixture was stirred overnight (18 hours) at 61°C, then formic acid was removed by evaporation *in vacuo* at 55°C and the residue was treated with 200 ml of 3-N sodium hydroxide. The mixture obtained was extracted with methylene chloride and the methylene chloride extract was evaporated *in vacuo* to give a yellow oil which was dissolved in 300 ml of ether/benzene (5:1). The solution was extracted with cold 5-N hydrochloric acid and the combined acid extracts were washed with benzene, neutralised with sodium hydroxide and extracted with methylene chloride. The methylene chloride extract was washed with water and evaporated *in vacuo* to give 2 - [N - (2 - bromo - ethyl) - N - methyl - amino] - 5 - chloro - benzophenone.

A solution of 2.6 g (7.35 mmol) of 2 - [N - (2 - bromo - ethyl) - N - methyl - amino] - 5 - chloro - benzophenone in 200 ml of ethanol saturated with ammonia was capped and allowed to stand at room temperature over the weekend. The solvent was then removed by evaporation *in vacuo* to leave a red gummy residue which was partitioned between 1-N sodium hydroxide and benzene. The benzene layer was separated and extracted with three 50 ml portions of 1-N hydrochloric acid. The combined acidic extracts were washed with benzene and made basic with sodium hydroxide. Extraction with benzene and removal of the solvent and water from the extract by evaporation *in vacuo* gave an oil which crystallized in petroleum ether (boiling
125 130

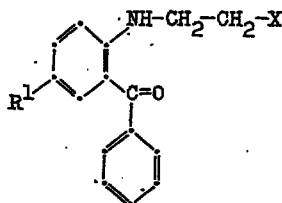
range 40°—60°C) to give 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine of melting point 100°—102°C.

5 WHAT WE CLAIM IS:—

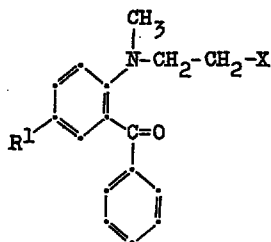
1. A process for the manufacture of compounds of the general formula



10 wherein R¹ represents a chlorine or bromine atom, which process comprises treating a 2 - amino - benzophenone derivative of the general formula



15 wherein R¹ has the significance given earlier in this claim and X stands for a chlorine, bromine or iodine atom, with a methylating agent and reacting the resulting 2 - methylamino - benzo - phenone derivative of the general formula



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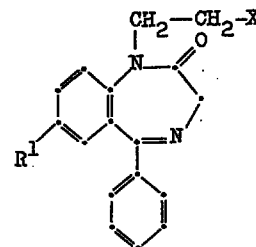
wherein R¹ and X have the significance given earlier in this claim, with ammonia.

25 2. A process as set forth in claim 1, wherein the methylating agent is a system comprising formaldehyde (or a substance which yields formaldehyde under the conditions of the treatment) and formic acid.

3. A process as set forth in claim 1 or in claim 2, wherein a 2 - amino - benzophenone

derivative in which R¹ represents a chlorine atom is used as the starting material. 30

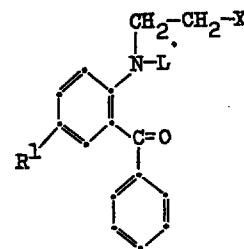
4. A process as set forth in any one of the preceding claims which includes the further and initial step of preparing the 2 - amino - benzophenone derivative of the formula second written in claim 1 by hydrolysing a benzdiaz - [1,4]epinone - (2) of the general formula 35



wherein R¹ and X have the significance given in claim 1. 40

5. A process as set forth in claim 4, wherein said benzdiaz[1,4]epinone - (2) is 7 - chloro - 1 - (2 - chloro - ethyl) - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2).

6. A process as set forth in any one of claims 1 to 3 inclusive which includes the further and initial step of preparing the 2 - amino - benzophenone derivative of the formula second written in claim 1 by heating a compound of the general formula 50



wherein R¹ and X have the significance given in claim 1 and L represents a nitrogen-protecting leaving group, in the presence of a proton-donating acid agent. 55

7. A process as set forth in claim 6, wherein 5 - chloro - 2 - [N - (2 - chloro - ethyl) - paratoluenesulphonamido] - benzophenone is used as the starting material.

8. A process as set forth in claim 6, wherein 5 - chloro - 2 - [N - (2 - bromo - ethyl) - paratoluenesulphonamido] - benzophenone is used as the starting material. 60

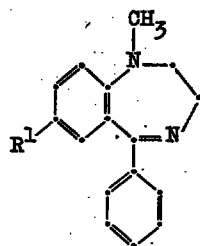
9. A process as set forth in claim 1, substantially as described with reference to the foregoing Examples. 65

10. Compounds of the formula first written in claim 1, when manufactured by the process claimed in any one of the preceding claims.

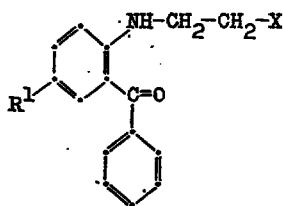
range 40°—60°C) to give 7 - chloro - 1 - methyl - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epine of melting point 100°—102°C.

5 WHAT WE CLAIM IS:—

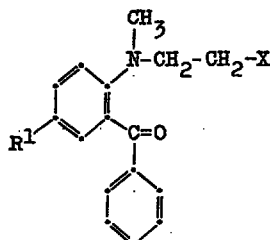
1. A process for the manufacture of compounds of the general formula



10 wherein R¹ represents a chlorine or bromine atom, which process comprises treating a 2 - amino - benzophenone derivative of the general formula



15 wherein R¹ has the significance given earlier in this claim and X stands for a chlorine, bromine or iodine atom, with a methylating agent and reacting the resulting 2 - methylamino - benzo - phenone derivative of the general formula



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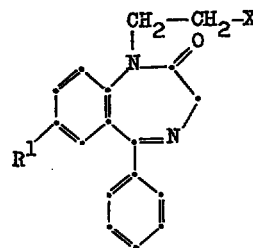
wherein R¹ and X have the significance given earlier in this claim, with ammonia.

25 2. A process as set forth in claim 1, wherein the methylating agent is a system comprising formaldehyde (or a substance which yields formaldehyde under the conditions of the treatment) and formic acid.

3. A process as set forth in claim 1 or in claim 2, wherein a 2 - amino - benzophenone

derivative in which R¹ represents a chlorine atom is used as the starting material. 30

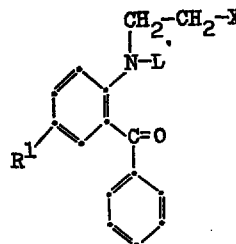
4. A process as set forth in any one of the preceding claims which includes the further and initial step of preparing the 2 - amino - benzophenone derivative of the formula second written in claim 1 by hydrolysing a benzdiaz - [1,4]epinone - (2) of the general formula 35



wherein R¹ and X have the significance given in claim 1. 40

5. A process as set forth in claim 4, wherein said benzdiaz[1,4]epinone - (2) is 7 - chloro - 1 - (2 - chloro - ethyl) - 5 - phenyl - 2,3 - dihydro - 1H - benzdiaz[1,4]epinone - (2).

6. A process as set forth in any one of claims 1 to 3 inclusive which includes the further and initial step of preparing the 2 - amino - benzophenone derivative of the formula second written in claim 1 by heating a compound of the general formula 50



wherein R¹ and X have the significance given in claim 1 and L represents a nitrogen-protecting leaving group, in the presence of a proton-donating acid agent. 55

7. A process as set forth in claim 6, wherein 5 - chloro - 2 - [N - (2 - chloro - ethyl) - *paratoluenesulphonamido*] - benzophenone is used as the starting material.

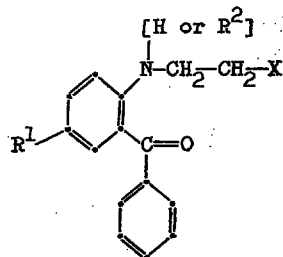
8. A process as set forth in claim 6, wherein 5 - chloro - 2 - [N - (2 - bromo - ethyl) - *paratoluenesulphonamido*] - benzophenone is used as the starting material. 60

9. A process as set forth in claim 1, substantially as described with reference to the foregoing Examples. 65

10. Compounds of the formula first written in claim 1, when manufactured by the process claimed in any one of the preceding claims.



11. A compound of the general formula



wherein R¹ and X have the significance given

in claim 1 and R² represents the methyl group.

12. A compound as formulated in claim 11, wherein R² is absent.

13. A compound as formulated in claim 11, wherein R² is present.

14. 5 - Chloro - 2 - (2 - chloro - ethyl - amino) - benzophenone.

15. 5 - Chloro - 2 - (2 - bromo - ethyl - amino) - benzophenone.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1968.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.

