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THE SYNTHESES OF 2- AND 4-TRIFLUOROMETHYL-CARBAZOLES VIA DIPHENYLAMINES

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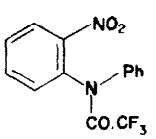
Abstract—Carbazoles, unsubstituted in the 9-position, have been prepared by applying the Pschorr reaction to N-acetyl-2-aminodiphenylamines. When applied to the preparation of carbazole itself and 2-trifluoromethylcarbazole the reaction was straightforward. When applied to the formation of 4-trifluoromethylcarbazole, the reaction gave the carbazole or the corresponding triazole or benziminazole depending upon the conditions used. It has been shown that the benziminazole can be formed by incorporating *one* of the nitrogen atoms of the diazonium intermediate into the heterocyclic ring. A mechanism is proposed for this novel reaction. 3-Trifluoromethyldiphenylamine has been prepared by standard methods.

N-ALKYL carbazoles can be made from N-alkyl *o*-aminodiphenyl amines by an application of the Pschorr reaction.[1,2] For the preparation of carbazoles unsubstituted on the nitrogen atom it is necessary to protect this atom with a group which obviously should be easily removable at the end of the synthesis. If no protecting group is employed the reaction leads to the formation of benzotriazoles. Using the acetyl group to protect the nitrogen during the formation of the carbazole system we have made 2- and 4-trifluoromethylcarbazole and carbazole itself.

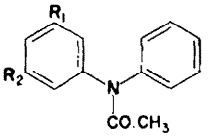
The easy hydrolysis of the N-trifluoroacetyl group has made it a useful protecting group in peptide synthesis,[3] and our first experiments were concerned with the use of this group. For the synthesis of carbazole itself, the intermediate N-trifluoroacetyl-2-nitrodiphenylamine (I) was made by warming the diphenylamine with trifluoroacetic anhydride without the use of a catalyst. The N-trifluoroacetyl derivative (I) could not however be reduced catalytically to the amine. Presumably a combination of the bulky phenyl and trifluoroacetyl groups prevents access of the catalyst to the nitro-group. Most useful chemical reductions are precluded since the conditions employed would lead to the hydrolysis of the N-trifluoroacetyl group.

It has been shown that N-acetyl carbazoles can be smoothly deacetylated with acid, alkali[4] or even lithium aluminium hydride.[5] Accordingly the acetyl group was employed as a blocking group in further experiments, the synthesis of carbazole itself used as a model. In contrast to the N-trifluoroacetyl derivative, N-acetyl-2-nitrodiphenylamine could easily be catalytically reduced to the amine. When N-acetyl-2-aminodiphenylamine was diazotized and the diazo-solution rendered alkaline,[1] N-acetyl carbazole could be isolated therefrom in a satisfactory yield (45 per cent) for this type of reaction.

[1] F. R. Storrie and S. H. Tucker, *J. Chem. Soc.* 2255 (1931).
[2] D. H. Hey and R. D. Mulley, *J. Chem. Soc.* 2276 (1952).
[3] F. Weygand and M. Reiher, *Chem. Ber.* **88**, 26 (1955).
[4] J. E. Saxton, *J. Chem. Soc.* 3593 (1952).
[5] V. M. Mićović and M. LJ. Mihailović, *J. Org. Chem.* **18**, 1190 (1953).

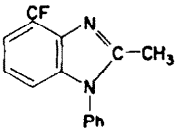


I



II : $R_1 = H, R_2 = CF_3$

III : $R_1 = CF_3, R_2 = H$



IV

For the synthesis of 2-trifluoromethyl carbazole we required the intermediate N-acetyl-2-amino-5-trifluoromethyldiphenylamine (II). This was prepared from 2-nitro-5-trifluoromethyldiphenylamine[6] by acetylating it with acetic anhydride in the presence of perchloric acid or zinc chloride and then reducing the nitro-group catalytically. The amine (II) was unstable and no attempt was made at purification. It was diazotized in a mixture of glacial acetic acid and dilute sulphuric acid, and the diazo-solution was warmed at 50–60° to complete the reaction. These conditions were somewhat limiting and were in fact worked out for the other trifluoromethyl isomer as will be described later. In the present instance they afforded N-acetyl-2-trifluoromethylcarbazole in 27 per cent yield. A comparison between this compound and that obtained by acetylating the carbazole which had been made from *m*-trifluorophenylhydrazine showed that they were identical.

N-Acetyl-2-amino-3-trifluoromethyldiphenylamine (III), the amine required for the preparation of 4-trifluoromethylcarbazole, was obtained from 2-nitro-3-trifluoromethyldiphenylamine by acetylation followed by reduction of the nitro-group. Attempts to convert the amine (III) into 4-trifluoromethylcarbazole were not immediately successful.

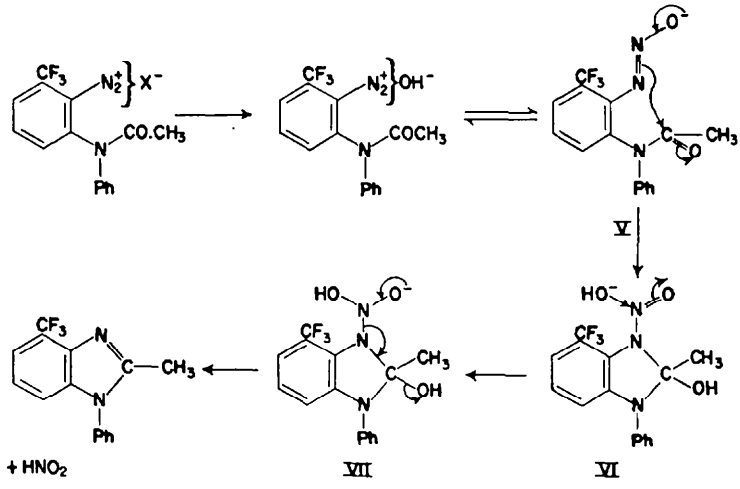
When the amine (III) was diazotized under normal conditions and the resulting solution treated with alkali, there was obtained an excellent yield of 2-methyl-1-phenyl-4-trifluoromethylbenziminazole (IV), whose structure was assigned from the following considerations. It analysed for $C_{15}H_{13}N_2F_3$ it was basic and formed stable salts with mineral acids. Its infra-red spectrum contained no band attributable to a carbonyl group, but a strong band at 1600 cm^{-1} could be assigned to a C=N group. In addition bands at 700 and 760 cm^{-1} served to indicate a mono-substituted phenyl group. Its ultra-violet spectrum differed significantly from those of carbazoles, but resembled that of benziminazole itself.[7] The formation of benziminazoles from acyldiphenylamines under acid conditions has been noted previously[8] and suggested that our compound had arisen during the dissolution of the diphenylamine in acid prior to diazotization. This was shown to be the case when the experiment was repeated without the intervention of sodium nitrite. The benziminazole was again obtained when the diazotization was attempted with nitrosyl sulphuric acid in glacial acetic acid. In this experiment the temperature was kept below 10° at all times. The ready formation of benziminazoles at room temperature is notable. In further experiments the temperature was kept below 20° and only dilute mineral acids were used.

When the diazotization was carried out in glacial acetic acid in the presence of N-sulphuric acid an orange colouration was produced in the solution. That diazotization had in fact taken place was confirmed with alkaline β-naphthol. After the

[6] Preceding Paper.
[7] K. Hofmann, *Imidazole and Its Derivatives* Part I, p. 253. Interscience, New York (1953).
[8] M. A. Philips, *J. Chem. Soc.* 2820 (1929).

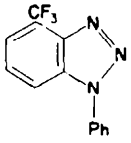
diazo-solution had been rendered alkaline, the benziminazole (IV) was again obtained. The yield (48 per cent) of benziminazole was surprisingly high and seemed to indicate that at least some of it must have been formed from the diazonium compound. This view was confirmed when the diazotized amine was coupled with β-naphthol. From a control experiment the azo-dye was obtained in 60 per cent yield of analytical purity, so that the yield of diazo-compound must have been much higher.

The formation of an iminazole ring from the diazo-compound signifies that one of its nitrogen atoms has been incorporated into the heterocyclic ring. This rupture of the diazo-linkage appears to have no parallel in the literature. The annexed scheme gives a possible mechanism for this novel reaction.



On the addition of alkali the diazonium salt is converted successively into hydroxide and then diazotate, which can ionize to give V. The proximity of the acetyl group, coupled with the ease with which it can undergo nucleophilic attack when attached to a weakly basic nitrogen atom, makes ring closure a favourable process. The acquisition of a proton then gives the intermediate VI. Attack by hydroxide ion, followed by the electronic shifts indicated in structure VII, complete the process. The resulting increase in aromaticity will provide the necessary driving force for the latter stages. That carbazole formation, the normal reaction, does not occur in this case may be ascribed to the *ortho*-trifluoromethyl group which will sterically hinder the formation of the transition state for carbazole formation much more so than that for the ring closure reaction. This steric effect is not pertinent to the formation of carbazole itself or the other trifluoromethyl isomer and no benziminazoles were encountered in their preparation. The formation of benziminazoles by the above mechanism implies that if the decomposition of the diazonium compound were carried out in acid solution no benziminazole would be formed. This indeed proved to be the case when the acid diazo solution was merely warmed to effect its decomposition. No basic material was formed in the reaction, from which 4-trifluoromethyl carbazole was isolated in 25 per cent yield. In an attempt to increase the yield of carbazole, the diazo-solution from amine (III) was made more strongly acidic by the addition of concentrated sulphuric acid before heating it. The sole product from this reaction

was 1-phenyl-4-trifluoromethyl triazole (VIII). Here the removal of the acetyl group may well take place after ring-closure has occurred.



VIII

Amides can behave as nucleophiles and this is well illustrated in our final experiment which was designed to eliminate the possibility, still present when we made this sample of 4-trifluoromethylcarbazole, that the material we had obtained was 3-trifluoromethyldiphenylamine and not the carbazole. The former compound was synthesized by condensing *m*-acetylaminotrifluoromethylbenzene with bromobenzene. Here the nucleophilic amide group displaces bromide ion an energetically less favourable reaction than triazole formation mentioned above, albeit under more strenuous reaction conditions. The infra-red spectrum of N-acetyl-3-trifluoromethyldiphenylamine shows bands at 707, 767 and 814 cm^{-1} which can be assigned to mono- and *meta*-substituted benzene rings. A band at 1695 cm^{-1} can be assigned to the amide group: this high frequency seems general for amides of weakly or non-basic amines and is found also for N-acetylcarbazoles. It is in the ultra-violet region that spectral differences are most striking. N-Acetyl-3-trifluoromethyldiphenylamine shows only a single band at 240 mμ and the diphenylamine itself a single band at 285 mμ. These contrast sharply with the complex spectra of the carbazoles and their N-acetyl derivatives. The benziminazole (IV) and triazole (VIII) spectra are again characteristic for these types of compound[7,9] and show marked differences when compared with those of carbazoles and diphenylamines.

EXPERIMENTAL

N-*Trifluoroacetyl-2-nitrodiphenylamine*

When 2-nitrodiphenylamine (1·5 g) was added to trifluoroacetic anhydride (10 g) a mild exothermic reaction ensued. When the reaction had subsided the mixture was boiled under reflux for 10 min and then evaporated under reduced press. The residual solid was recrystallized from aqueous ethanol to afford N-*trifluoroacetyl-2-nitrodiphenylamine* (1·55 g, 71%) in leaflets, m.p. 112° (Found: C, 54·3; H, 3·0. $C_{14}H_9O_3N_2F_3$ requires: C, 54·2; H, 2·9%).

N-*Acetyl-2-aminodiphenylamine*

N-acetyl-2-nitro-diphenylamine was made by warming the diphenylamine with acetic anhydride in the presence of zinc chloride. A solution of the N-acetyl compound (1·0 g) in ethanol (20 cc) was shaken under hydrogen at room temp and press with Raney nickel (ca. 0·5 g). When hydrogen uptake had ceased (ca. 1·5 hr), the solution was filtered and evaporated to dryness. The residual solid was recrystallized from aqueous ethanol to afford N-*acetyl-2-aminodiphenylamine* as colourless leaflets (0·8 g), m.p. 115–116° (Found: C, 74·3; H, 5·9. $C_{14}H_{14}ON_2$ requires: C, 74·1; H, 6·2%). Its hydrochloride had m.p. 210–211° after recrystallization from ether–ethanol.

The *picrate* crystallized with difficulty from amyl alcohol in small yellow needles, m.p. 222–223° (decomp) (Found: C, 56·2; H, 3·4. $C_{20}H_{17}ON_5$ requires: C, 56·6; H, 3·4%).

N-*Acetylcarbazole*

A solution of N-acetyl-2-aminodiphenylamine hydrochloride (2·0 g) in conc HCl (10 cc) at 0° was treated with a solution of sodium nitrite (0·6 g) in water (3 cc). The mixture was stirred for

[9] Mme. Ramart-Lucas and J. Hoch, *Bull. Soc. Chim. Fr.* [5], **16**, 447 (1949).

15 min after the addition of the nitrite solution and then rendered alkaline by the rapid addition of 4 N-KOH, when a dark-coloured solid separated almost immediately. The solid was collected, dried *in vacuo* and then boiled in ether with charcoal. The filtered solution was evaporated to afford a residue which crystallized from benzene–light petroleum (b.p. 40–60°). Recrystallization from light-petroleum (b.p. 40–60°) afforded colourless needles (0·75 g, 45%) of N-acetylcarbazole, m.p. 69–70°, undepressed on admixture with an authentic specimen.

N-*Acetyl-2-nitro-5-trifluoromethyldiphenylamine*

A solution of 5-trifluoromethyl-2-nitrodiphenylamine (1·5 g)[6] in acetic anhydride (10 cc) containing 60% perchloric acid (1 drop) was maintained at 50° for 1 min. During this time the colour of the solution changed from orange-red to pale yellow. On pouring the solution into ice-cold water (50 cc) a precipitate was formed. The solid was collected at the pump, washed with aqueous potassium carbonate, then with water and dried *in vacuo*. Recrystallization from ether–light petroleum (b.p. 40–60°), followed by recrystallization from light petroleum (b.p. 40–60°) afforded N-*acetyl-2-nitro-5-trifluoromethyldiphenylamine* as pale-yellow prisms (1·5 g, 87%), m.p. 62–63° (Found: C, 55·8; H, 3·4; F, 17·4. $C_{15}H_{11}O_3N_2F_3$ requires: C, 55·6; H, 3·4; F, 17·6%).

When the diphenylamine (0·2 g) in acetic anhydride (5 cc) containing a trace of zinc chloride was warmed at 70–75° for 5 min, and the product worked up as described above, the N-acetyl compound was obtained in 78% yield.

N-*Acetyl-2-amino-5-trifluoromethyldiphenylamine*

A solution of N-acetyl-2-nitro-5-trifluoromethyldiphenylamine (0·2 g) in ethanol (15 cc) was shaken under hydrogen at room temp and press with 8% palladized charcoal (0·1 g). When hydrogen uptake was complete (ca. 2 hr) the solution was filtered and evaporated to dryness to give the amine as a colourless solid (0·16 g), m.p. 63–65°. The amine could not be recrystallized and was used in subsequent reactions without further purification.

N-*Acetyl-2-trifluoromethylcarbazole*

Ice-cold N H_2SO_4 (1 cc) was added to a cooled solution of N-acetyl-2-amino-5-trifluoromethyldiphenylamine (0·16 g) in glacial acetic acid (2 cc). Whilst the temp was kept below 5°, this solution was treated with sodium nitrite (0·08 g) in water (2 cc). After being stirred for 15 min the solution was warmed at 50–60° for 15 min. A copious evolution of nitrogen accompanied the separation of an oil. Water (40 cc) was then added to the mixture which was set aside at room temp for 2 hr. The aqueous layer was decanted and the residual oil taken up in ether (25 cc). The ethereal extract was washed with N Na_2CO_3, dried and evaporated. The residual gum (0·16 g) was taken up in benzene–light petroleum (1 : 10) and chromatographed on neutral alumina (15 × 1 cm). Elution with benzene–light petroleum (1 : 20) afforded a solid which crystallized from light petroleum (b.p. 60–80°). N-Acetyl-2-trifluoromethylcarbazole was thereby obtained in small prisms (0·025 g, 27%), m.p. 122–123°, undepressed on admixture with an authentic specimen.[6] The infra-red spectra show a carbonyl band at 1716 cm^{-1} (KBr disk), and are otherwise identical.

N-*Acetyl-2-nitro-3-trifluoromethyldiphenylamine*

2-Nitro-3-trifluoromethyldiphenylamine (1·5 g),[6] acetic anhydride (10 cc) and a small piece of anhydrous zinc chloride were maintained at 60–70° for 20 min. The mixture was then poured into water and extracted with ether (3 × 25 cc). The combined extracts were washed with aqueous sodium carbonate, dried, treated with charcoal and evaporated. Recrystallization of the residual solid from ethanol afforded long pale-yellow needles of N-*acetyl-2-nitro-3-trifluoromethyldiphenylamine* (1·5 g), m.p. 96–97° (Found: C, 55·8; H, 3·6. $C_{15}H_{11}O_3N_2F_3$ requires: C, 55·6; H, 3·4%).

N-*Acetyl-2-amino-3-trifluoromethyldiphenylamine*

A solution of N-acetyl-2-nitro-3-trifluoromethyldiphenylamine (1·4 g) in ethanol (25 cc) was shaken under hydrogen at room temp and press with Raney nickel. When hydrogen uptake was complete (2·5 hr) the solution was filtered and evaporated. When the residual solid was recrystallized

from ethanol N-*acetyl*-2-*amino*-3-*trifluoromethyldiphenylamine* was obtained in colourless prisms (0·8 g), m.p. 153–154° (Found: C, 60·9; H, 4·2. $C_{15}H_{13}ON_2F_3$ requires: C, 61·2; H, 4·4%).

2-Methyl-1-phenyl-4-trifluoromethylbenziminazole

A mixture of N-acetyl-2-amino-3-trifluoromethyldiphenylamine (0·2 g), conc HCl (2 cc) and water (2 cc) was heated at 75–80° for 2–3 min. The cooled solution was poured into water (20 cc) and rendered alkaline by the addition of 4 N KOH. The precipitated solid was collected at the pump, washed with water, dried *in vacuo* and recrystallized from light petroleum (b.p. 80–100°). *2-Methyl-1-phenyl-4-trifluoromethylbenziminazole* was thus obtained in colourless glistening plates (0·14 g), m.p. 143° (Found: C, 64·7; H, 3·7; F, 20·5. $C_{15}H_{11}N_2F_3$ requires : C, 65·2; H, 4·0; F, 20·7%).

The infra-red spectrum (KBr disc) shows bands at 1600 (C=N stretching), 700 and 760 (mono-substituted benzene ring) cm^{-1}. Light absorption in ethanol: λ_{max} 240, 256, 279 and 287 mμ; log ϵ 3·9, 3·94, 3·86 and 3·85 respectively.

The *hydrochloride*, obtained by treating an ethereal solution of the base with hydrogen chloride, crystallized from ethanol–ether in colourless leaflets, m.p. 215° (decomp) (Found: C, 57·5; H, 4·0. $C_{15}H_{12}N_2F_3Cl$ requires: C, 57·6; H, 3·8%).

Diazotization of N-*acetyl*-2-*amino*-3-*trifluoromethyldiphenylamine*

(a) A solution of the amine (0·2 g) in glacial acetic acid (2 cc) was cooled rapidly to below 5°. Ice-cold 2 N H_2SO_4 (2 cc) was then added dropwise to the solution, followed immediately by a cold solution of sodium nitrite (0·08 g) in water (2 cc), when the colour of the solution deepened. After standing for 15 min at 0°, the solution was rendered alkaline by the addition of 4 N KOH, the temp being kept below 10°. A solid separated from the mixture which was stirred for 15 min and extracted with ether (3 × 25 cc). The combined extracts were dried and evaporated. The residual solid was taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (2 : 5) and chromatographed on neutral alumina (10 × 1 cm). Elution with benzene afforded 2-methyl-1-phenyl-4-trifluoromethyl-benziminazole, obtained as colourless prisms (0·06 g, 48%) from light petroleum (b.p. 60–80°), m.p. 143° undepressed on admixture with an authentic specimen.

(b) After the amine (0·1 g) had been diazotized as described in (a), the diazo-solution was added dropwise to a solution of β-napththol (0·2 g) in 4 N KOH (20 cc) at 5°. After the mixture had stood for 15 min, the deep-red solid was collected at the pump, washed with water and dried *in vacuo*. It was then taken up in benzene and chromatographed on neutral alumina (20 × 1 cm). Elution with the same solvent afforded N-*acetyl*-2-(1-*azo*-2-*naphthol*)-3-*trifluoromethyldiphenylamine*, which crystallized from aqueous methanol in small deep-red needles (0·09 g, 60%), m.p. 152–153° (Found: C, 66·8; H, 4·2; F, 12·4. $C_{25}H_{18}O_2N_3F_3$ requires: C, 66·8; H, 4·0; F, 12·7%).

(c) Ice-cold N H_2SO_4 (2 cc) was added dropwise to a solution of the amine (0·5 g) in glacial acetic acid (8 cc). On the addition of a solution of sodium nitrite (0·2 g) in water (2 cc) the mixture assumed an orange-yellow colour and gave a precipitate with alkaline β-naphthol. After being stirred for 20 min, the solution was treated with conc H_2SO_4 (3 cc) and stirred for a further 10 min. The mixture was then heated at 50–60° for 45 min when a colourless precipitate was formed. After being diluted to 50 cc with water, the mixture was left in a refrigerator for 24 hr. The solid was then collected at the pump, washed with water and dried. Recrystallization from aqueous acetic acid afforded 1-phenyl-4-trifluoromethylbenzotriazole in colourless leaflets (0·17 g, 38%), m.p. 152–153° undepressed on admixture with an authentic specimen.[6] Light absorption in ethanol: λ_{max} 272 mμ, log ϵ 3·94.

The filtrate, obtained after removing the benzotriazole, was rendered alkaline with aqueous potassium hydroxide. The precipitated solid was collected and dried. Recrystallization from light petroleum afforded colourless prisms (0·31 g) of 2-methyl-1-phenyl-4-trifluoromethylbenziminazole, m.p. 143°, undepressed on admixture with an authentic specimen.[6]

(d) A solution of the amine (0·25 g) in glacial acetic acid (5 cc) was cooled to 5° and treated dropwise with ice-cold N H_2SO_4 (2 cc) followed by a solution of sodium nitrite (0·12 g) in water (3 cc). The yellow diazo-solution was stirred for 15 min at 0° and then warmed on a water-bath at 60–70° for 30 min, whilst nitrogen was evolved. After being stored in ice for several hours the solution was filtered. The residue was dried, taken up in a mixture of benzene and light petroleum (b.p. 60–80°) (1 : 1), and chromatographed on neutral alumina (15 × 1 cm). Elution with benzene–light petroleum (20 : 1) then afforded N-acetyl-4-trifluoromethylcarbazole as colourless leaflets

(0·035 g, 29%) after recrystallization from aqueous acetic acid: m.p. 94–95°, undepressed on admixture with an authentic specimen.[6] Its solution in ethanol fluoresced strongly in ultra-violet light and showed absorption bands at λ_{max} 261, 292 and 320 mμ, log ϵ 4·09, 4·16 and 3·78 respectively.

N-Acetyl-3-trifluoromethyldiphenylamine

An anhydrous mixture of *m*-acetylaminotrifluoromethylbenzene (10 g), nitrobenzene (75 cc), bromobenzene (30 cc), potassium carbonate (5 g), cuprous iodide (1 g) and copper bronze (1 g) was stirred vigorously and boiled under reflux for 24 hr. The mixture was then distilled in steam and the distillate discarded. The non-volatile solid was collected at the pump and extracted with boiling ether (100 cc). Evaporation of the ethereal extract afforded a semi-solid residue, which on treatment with light petroleum (b.p. 60–80°) containing a little benzene afforded *m*-acetylaminotrifluoromethylbenzene (3 g) as a crystalline solid. The mother liquors from this operation were then evaporated and the residue therefrom was taken up in benzene–light petroleum (1 : 4) and chromatographed on neutral alumina (3 × 20 cm). Elution with benzene afforded a solid which after crystallization from light petroleum (b.p. 60–80°) gave *N-acetyl-3-trifluoromethyldiphenylamine* (4·0 g, 29%) in colourless prisms, m.p. 53–54° (Found: C, 64·6; H, 4·1. $C_{15}H_{12}ONF_3$ requires: C, 64·5; H 4·3%). Light absorption in ethanol: λ_{max} 240 mμ, log ϵ 4·02. The infra-red spectrum (KBr) shows bands at 1695, 814, 767 and 707 cm^{-1}.

3-Trifluoromethyldiphenylamine

A solution of N-acetyl-3-trifluoromethyldiphenylamine (0·5 g) in ethanol (10 cc) and conc HCl (10 cc) was heated under reflux for 2·5 hr. The dark-coloured liquid was then poured into water (100 cc) and the mixture extracted with ether (2 × 25 cc). The combined ethereal extracts were dried and distilled twice at 15 mm. *3-Trifluoromethyldiphenylamine* was thereby obtained as a colourless oil (0·4 g, 95%) (Found: C, 65·7; H, 4·3; F, 24·0. $C_{13}H_{10}NF_3$ requires: C, 65·8; H, 4·2; F, 24·4%). The amine rapidly darkens in air. Light absorption in ethanol: λ_{max} 285 mμ, log ϵ 4·05. The infra-red (liquid film) shows a band at 3510 cm^{-1} (N—H stretching).

Acknowledgements—We thank Professors M. Stacey, F.R.S., and J. C. Tatlow for their interest and encouragement, and Ciba Limited, Basle, for the award of a scholarship (to R. T. W.).