Tetrahedron, 1960, Vol. 8, pp. 67 to 72. Pergamon Press Ltd. Printed in Northern Ireland

THE SYNTHESIS OF 1-, 2- AND 3-TRIFLUOROMETHYLCARBAZOLES BY THE FISCHER–INDOLE METHOD

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(*Received* 28 *July* 1959)

Abstract—1-, 2-, and 3-Trifluoromethylcarbazoles have been obtained from the corresponding tetrahydrocarbazoles, which were made by the Fischer-indole method. Cyclization of cyclohexanone-*m*-trifluoromethylphenylhydrazone gave only one tetrahydrocarbazole: this afforded 2-trifluoromethylcarbazole.

THE biological activity of compounds containing the trifluoromethyl group has hardly been studied. We decided therefore to make a number of trifluoromethylanalogues of heterocyclic compounds of biological importance. Our first efforts, directed towards analogues of tryptophane and serotonin, were unsuccessful. The difficulty of obtaining suitable tri-substituted benzenes, containing the trifluoromethyl group, and the general instability of the trifluoromethyl group towards Lewis acids makes the Fischer–indole route the most reasonable approach to these compounds. However, the deactiviting effect of the trifluoromethyl group on the benzene nucleus either precludes the formation of simple indoles or renders their formation very difficult by this method. The phenylhydrazones of cyclohexanone however usually cyclize more readily than those of other carbonyl compounds, and in this respect the trifluoromethylphenylhydrazones were not exceptional. They afforded fairly good yields of tetrahydrocarbazoles from which were obtained 1-, 2-, and 3-trifluoromethyl carbazoles.

m-Trifluoromethylphenylhydrazine, the most accessible member of the series, was obtained by a modification of the method of Bornstein *et al.*[1] It formed with cyclohexanone a hydrazone which proved to be very unstable in light and air, but which on treatment with acid gave a good yield of only one tetrahydrocarbazole (I), whose ultraviolet spectrum closely resembled that of tetrahydrocarbazole itself. Dehydrogenation of the tetrahydrocarbazole failed using Raney nickel, but proceeded smoothly with chloranil in boiling xylene. The carbazole produced was shown later by an unequivocal synthesis[2] to be the 2-trifluoromethyl isomer; a comparison being made between their N-acetyl derivatives. The acetylation of 2-trifluoromethylcarbazole, as with the other isomers, proceeded smoothly with acetic anhydride, when catalytic amounts of zinc chloride or perchloric acid,[3] but not sulphuric acid were used.

The preparations of *o*-, and *p*-aminotrifluoro methylbenzenes are somewhat tedious. Of the several methods available[4–6] for the preparation of the *para* isomer, perhaps the most convenient is that of Pouterman and Girardet.[5] It involves the

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[1] J. Bornstein, S. A. Leone, W. F. Sullivan and A. F. Bennett, *J. Amer. Chem. Soc.* **79**, 1745 (1957).

[2] Succeeding Paper: *Tetrahedron* **8**, 73 (1960).

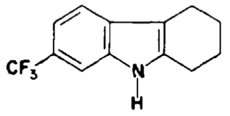
[3] F. Kehrmann and E. Baumgartner, *Helv. Chim. Acta* **9**, 673 (1926); A. A. Berlin, *Chem. Abstr.* **39**, 4606 (1945).

[4] R. G. Jones, *J. Amer. Chem. Soc.* **69**, 2346 (1947).

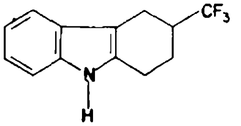
[5] E. Pouterman and A. Girardet, *Helv. Chim. Acta.* **30**, 107 (1947).

[6] Brit. Pat., 459881 and 459,890.

deamination of 3-amino-4-nitrotrifluoromethylbenzene followed by reduction of the nitro compound. Reduction of the diazonium salt from *p*-aminotrifluoromethylbenzene with ammonium sulphite gave a much better yield (79 %) of *p*-trifluoromethylphenylhydrazine than did that using stannous chloride (43 %). This is in keeping with the fact that in general the reduction of diazonium ions containing powerful electron withdrawing substituents in the *ortho-* or *para*-positions gives low yields of hydrazine using stannous chloride.[7] The preparation of cyclohexanone-*p*-trifluorophenylhydrazone and its conversion into 6-trifluoromethyltetrahydrocarbazole proceeded normally. Again dehydrogenation of the tetrahydro compound succeeded with chloranil but not with Raney nickel. 3-Trifluoromethylcarbazole thereby obtained was shown to be identical with a specimen obtained by the dehydrogenation of 3-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (II) obtained from the phenylhydrazone of 4-trifluoromethylcyclohexanone.[8]



I



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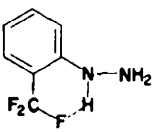

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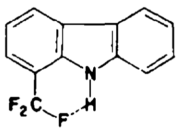

IV

o-Trifluoromethylaniline was obtained from *m*-acetamidotrifluoromethylbenzene. Nitration of this compound[9] with fuming nitric acid in sulphuric acid gave 5-amino-2-nitrotrifluoromethylbenzene after subsequent hydrolysis of the product with 50 per cent sulphuric acid. Hydrolysis of the amide with alkali[9] afforded a much inferior yield of amine. Deamination of the amine was best effected by a modification of the method of Hodgson and Turner.[10] The amine was diazotized with ethyl nitrite and the diazonium salt was reduced with copper bronze in ethanol to give a high yield of *o*-nitrotrifluoromethylbenzene. Reduction of this nitro-compound with Raney nickel and the subsequent conversion of *o*-trifluoromethylaniline into *o*-trifluoromethylphenylhydrazine proceeded normally. Again the use of ammonium sulphite at pH 6–7 rather than stannous chloride under acid conditions gave a better yield of hydrazine from the diazonium compound.

o-Trifluoromethylphenylhydrazine reacts more slowly with carbonyl compounds than do the other isomers. Steric effects may well be operative, but the compound is probably a weaker base than the other hydrazines due to possible intramolecular hydrogen bonding (III). Cyclization of its anil with cyclohexanone gave 8-trifluoromethyl-1,2,3,4-tetrahydrocabrazole as a liquid, which could not be induced to crystallize. In this respect it differs from the other members of the series which are fairly high

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[7] K. H. Saunders, *The Aromatic Diazo-compounds* (2nd Ed.) pp. 184–185. Edward Arnold, London (1949).

[8] F. L. Turner, Ph.D. Thesis, Birmingham University (1958).

[9] H. Rouche, *Bull. Sci. Acad. Roy. Belg.* [5], **13**, 346 (1927).

[10] H. H. Hodgson and H. S. Turner, *J. Chem. Soc.* 10 (1944).

melting solids. Moreover it was appreciably less stable towards heat than the other tetrahydro-compounds, and its dehydrogenation to 1-trifluoromethylcarbazole proved difficult. The usual agents—Raney nickel, palladized charcoal or chloranil—gave either starting material or decomposition products. Success was finally achieved using sulphur in boiling quinoline, a method previously used in this series by Plant and Oakeshott.[11] Again, 1-trifluoromethylcarbazole (IV) is a much lower melting solid than the other members of this series, and surprisingly it deteriorates on keeping. These results and those for the tetrahydro-compound may well be due to hydrogen bonding, illustrated for the carbazole itself (IV). Apart from its elemental analysis, its ultra-violet spectrum and its colour reactions leave no doubt that it is a carbazole. The ultra-violet spectra of the tetrahydrocarbazoles closely resemble that of the parent compound but display a small bathochromic shift. The ultra-violet spectra of the carbazoles all resemble that of carbazole itself with a characteristic series of bands.

EXPERIMENTAL

Ultra-violet spectra were measured in ethanol.

m-*Trifluorophenylhydrazine*

The hydrogenation of *m*-nitrotrifluoromethylbenzene in methanol using Raney nickel catalyst at 100°/100 atm afforded *m*-aminotrifluoromethylbenzene (92%), b.p. 79–82°/15 mm. A solution of sodium nitrite (82 g) in water (160 cc) was added to a vigorously stirred suspension of amine hydrochloride [from amine (147 g)] in a mixture of conc HCl (400 cc) and water (270 cc) at 5°. After 15 min the diazo-solution was poured slowly with stirring into a solution of stannous chloride dihydrate (530 g) in conc HCl (530 cc). After being stirred for a further 10 min, the solution was diluted with water, filtered and then rendered alkaline with 4 N NaOH. After working up the mixture in the usual manner *m*-trifluorophenylhydrazine was obtained as a pale-yellow liquid (110 g, 69%), b.p. 138–140°/14 mm Bornstein *et al.*[1] cite b.p. 80–83°/9 mm.

The *hydrochloride* was obtained by treating an ethereal solution of the base with dry hydrogen chloride. It crystallized in leaflets from ethyl acetate-light petroleum, m.p. 224–225° (decomp) (Found: C, 39·5; H, 3·9; F, 27·2. $C_7H_8N_2F_3Cl$ requires: C, 39.5; H, 3·8; F, 26·9%).

The *benzoyl* derivative, made by the Schotten-Baumann method crystallized from ethanol in long needles, m.p. 178–179° (Found: C, 59·6; H, 3·8. $C_{14}H_{11}N_2OF_3$ requires: C, 60·0; H, 3·9%).

The *benzylidene* derivative, prepared in methanol, crystallized from methanol as a yellow microcrystalline solid, m.p. 89–90° (Found: C, 63·7; H, 4·1. $C_{14}H_{11}N_2F_3$ requires: C, 63·7; H, 4·2%).

7-*Trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole*

When *m*-trifluoromethylphenylhydrazine hydrochloride (1·0 g) in methanol (2 cc, containing a drop of HCl) was treated with cyclohexanone (0·5 g) a vigorous exothermic reaction ensued. The yellow precipitate so formed was recrystallized several times from methanol (charcoal) to afford colourless needles of the *m*-trifluorophenylhydrazone (0·6 g), m.p. 139°. It was unstable in light and air and could not be analysed.

A mixture of the hydrazone (0·5 g), conc H_2SO_4 (1·0 cc) and glacial acetic acid (6·0 cc) was maintained at 75–85° for 30 min. On pouring the cooled solution into water, a precipitate was formed. This was filtered off, washed with water, and recrystallized from ethanol to give colourless plates of 7-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (0·3 g), m.p. 124–127°. It decomposed rapidly in light and air and could not be analysed.

Light absorption: λ_{max} 292 mμ, log ε_{max} 3·69.

2-*Trifluoromethylcarbazole.*

A solution of 7-trifluoromethyl-1,2,3,4-tetrahydrocarbazole (0·75 g) and chloranil (1·5 g, 2 moles) in a minimum of sulphur-free xylene was boiled under reflux until the liquid no longer gave a red colour with warm 2 N NaOH (ca. 4 hr).

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[11] S. H. Oakeshott and S. G. P. Plant, *J. Chem. Soc.* 1210 (1926).

The cooled solution was filtered and, after being diluted with ether, was washed several times with 2 N NaOH and finally with water. It was dried and evaporated to leave a semi-solid residue which sublimed at 120°/0·1 mm. Recrystallization of the sublimate from benzene afforded colourless leaflets of *2-trifluoromethylcarbazole*, (0·3 g), m.p. 209–210° (Found: C, 66·7; H, 3·4; F, 23·8. $C_{13}H_8NF_3$ requires: C, 66·4; H, 3·5; F, 24·2%). Light absorption: λ_{max} 234, 236, 238, 249, 258 and 295 mμ.

The N-acetyl derivative was made by heating a mixture of the carbazole (0·1 g) and a catalytic amount of anhydrous zinc chloride in acetic anhydride (3 cc) for 20 min. The cooled solution was poured into water (20 cc) and the mixture was worked up in the usual manner to afford the N-acetyl derivative as small colourless needles from light petroleum (b.p. 60–80°), m.p. 122–123°, undepressed on admixture with an authentic specimen[2] (Found: C, 65·0; H, 3·5. $C_{15}H_{10}ONF_3$ requires: C, 65·0; H, 3·6%). Light absorption: λ_{max} 267, 287, 306 and 318 mμ; log ε 4·2, 4·16, 3·76 and 3·8 respectively.

p-*Aminotrifluoromethylbenzene*

(a) A solution of *p*-nitrotrifluoromethylbenzene (51·0 g) in light petroleum (b.p. 40–60°) was hydrogenated at 100°/100 atm using Raney nickel catalyst. When reduction was complete (ca. 4 hr) the mixture was worked up in the usual manner to afford the amine (30 g), b.p. 85–88°/16 mm.

(b) An intimate mixture of N-(*p*-trichloromethylphenyl) phthalimide (92 g)[6] and antimony trifluoride (48 g) was melted and gently heated under reflux for a further 10 min. The cooled mixture was extracted with boiling ethanol (250 cc) and the extract was poured into dil HCl. The resultant precipitate was treated with 6 N HCl, and the mixture was filtered. A solution of the residue in boiling ethanol was poured into cold water. After standing for 2 hr at 0°, the trifluoro–imide was obtained as a pale-yellow solid, m.p. 128–131° (30 g, 38%). The trifluoro-imide (100 g) was heated in a current of steam with 12% hydrazine hydrate (230 cc) for 12 hr. Working up the distillate in the usual manner gave *p*-aminotrifluoromethylbenzene (15 g, 27%), b.p. 86–88°/15 mm. When the trichloro-compound was treated with liquid hydrogen fluoride,[6] the trifluoro-imide was obtained in only 15% yield.

p-*Trifluoromethylphenylhydrazine*

(a) *p*-Aminotrifluoromethylbenzene was diazotized and the diazo-compound reduced with stannous chloride as for the *meta*-isomer. A solution of the hydrazine, so obtained, in ether was treated with anhydrous hydrogen chloride to give p-*trifluoromethylphenylhydrazine hydrochloride* as a colourless solid which crystallized from ethanol–ether in leaflets (1·2 g, 43%), m.p. 206–207° (decomp) (Found: C, 39·2; H, 3·3; F, 27·0. $C_7H_8N_2F_3Cl$ requires: C, 39·5; H, 3·7; F, 26·9%).

(b) A fine suspension of amine hydrochloride [from amine (11·0 g)] in conc HCl (20 cc) was treated with a solution of sodium nitrite (6·0 g) in water (24 cc) at 0–5°. After 15 min the diazo-solution was brought to pH 6·5 with N Na_2CO_3 and poured rapidly into a solution of ammonium sulphite (60 cc, made by saturating aqueous ammonia, *d* 0·880, with sulphur dioxide at 0°) keeping the temperature below 5°. The solution was stirred for 1 hr at room temp and was then heated on a steam-bath with conc HCl (25 cc) until no more sulphur dioxide was evolved. After boiling it under reflux the solution was cooled and rendered alkaline with 4 N NaOH (cooling). The mixture was extracted with ether and worked up in the usual manner to afford *p*-trifluoromethylphenylhydrazine (9·5 g, 79%) as long colourless needles from light-petroleum (b.p. 40–60°), m.p. 59–60°, whose hydrochloride was identical with that prepared by method (a).

The *benzylidene* derivative, prepared in methanol, crystallized from methanol in colourless needles, m.p. 129–130° (Found: C, 63·3; H, 4·2. $C_{14}H_{11}N_2F_3$ requires: C, 63·7; H, 4·2%).

6-*Trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole*

A mixture of *p*-trifluoromethylphenylhydrazine (1·0 g), cyclohexanone (1·0 g) and ethanol (4 cc) containing conc HCl (2 drops) was heated on a water bath for 1 min. The precipitate was collected, washed with water and recrystallized from methanol to give small yellow needles of cyclohexanone-*p*-trifluoromethylphenylhydrazone, m.p. 155–158° (too unstable for analysis).

A solution of the hydrazone (1·0 g) in conc H_2SO_4 (1·0 cc) and glacial acetic acid (6·0 cc) was heated on a steam bath for 30 min. The cooled solution was diluted with water (100 cc) and filtered. The solid was collected, washed with water and dried. It distilled at 140–142°/0·1 mm to give a pale-yellow distillate which solidified in the receiver. The distillate crystallized from light-petroleum (b.p. 60–80°) to afford 6-*trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole* as colourless glistening needles (0·5 g, 40%), m.p. 83–84° (Found: C, 65·4; H, 5·0. $C_{13}H_{12}NF_3$ requires: C, 65·3; H, 5·0%). Light absorption: λ_{max} 283 mμ, log ε 4.37.

3-*Trifluoromethylcarbazole*

A solution of chloranil (0·8 g) and the tetrahydro-compound (0·4 g) in purified xylene was boiled under reflux until it no longer gave a colour with warm 2 N NaOH (ca. 6 hr). The cooled solution was filtered and diluted with ether. After being shaken several times with 2 N NaOH, the organic phase was dried and evaporated. On heating at 115°/0·1 mm, the residue sublimed to give 3-*trifluoromethylcarbazole* as a solid, which crystallized from light petroleum (b.p. 80–100°) in colourless needles, m.p. 166–167° (Found: C, 66·2; H, 3·7. $C_{13}H_8NF_3$ requires: C, 66·4; H, 3·4%). The compound showed no m.p. depression on admixture with a specimen obtained from the phenylhydrazone of 4-trifluoromethylcyclohexanone.[8] Light absorption: λ_{max} 236, 262, 295, 312 and 320 mμ; log ε 3·87, 3·81, 3·31, 2·67 and 2·81.

5-*Amino-2-nitrotrifluoromethylbenzene*

A mixture of fuming nitric acid (76 cc) and conc H_2SO_4 (130 cc) was added with stirring to a solution of *m*-acetylaminotrifluoromethylbenzene (255 g) in conc H_2SO_4 (1360 cc) over a period of 45 min, the temp being kept below 5°. After standing for 15 hr at room temp, the mixture was warmed at 40° for 1 hr, and was then poured on to crushed ice (ca. 4 kg). 5-Acetylamino-2-nitrotrifluoromethylbenzene was thereby obtained as a yellow solid (270 g).

A mixture of the acetyl compound (100 g), conc H_2SO_4 (283 cc) and water (480 cc) was heated on a steam-bath for 2 hr, and then boiled for 1 hr. On pouring the cooled solution into water at 0°, 5-amino-2-nitrotrifluoromethylbenzene was obtained as a solid, which crystallized from aqueous-ethanol in yellow needles (60 g, 70%), m.p. 124–126°.

2-*Nitrotrifluoromethylbenzene*

5-Amino-2-nitrotrifluoromethylbenzene (57·8 g) was added with stirring to a solution of conc H_2SO_4 (31 cc) in ethanol (225 cc) at 0°. Ethyl nitrite (42 g) was added with cooling over 1 hr to the suspension of amine sulphate thus formed. After standing for 1 hr at 5°, the solution was allowed to come to room temp and was then treated with copper bronze (0·45 g). Evolution of nitrogen then ensued smoothly for ca. 2 hr, while the temp of the solution was kept below 40°. After being boiled for 15 min, the solution was cooled and diluted with water. The organic phase was separated and added to the combined chloroform extracts (4 × 100 cc) of the aqueous layer. Removal of the solvents and distillation of the residue afforded 2-nitrotrifluoromethylbenzene (43·7 g, 82%), b.p. 100–102°/15 mm, m.p. 28–30°.

When 5-amino-2-nitrotrifluoromethylbenzene was deaminated according to the method of Hodgson and Turner[10] the yield of 2-nitrotrifluoromethylbenzene was 40%.

o-*Aminotrifluoromethylbenzene*

A solution of 2-nitrotrifluoromethylbenzene (160 g) in light petroleum (b.p. 60–80°) was hydrogenated at 120°/100 atm using Raney nickel catalyst (ca. 10 g). The filtered solution was distilled to yield *o*-aminotrifluoromethylbenzene (111 g, 82%) as a colourless liquid, b.p. 77–80°/15 mm.

o-*Trifluoromethylphenylhydrazine*

A stirred suspension of *o*-aminotrifluoromethylbenzene hydrochloride [from amine (5·5 g)] in conc HCl (10 cc) and water (5 cc) was treated with a solution of sodium nitrite (3·0 g) in water (6·0 cc) at 0°. After being kept for 15 min, the diazo-solution was added slowly to a solution of ammonium sulphite (30 cc) at 0–5°. When the mixture had stood for 20 min, it was treated with conc HCl (20 cc) and boiled until the evolution of sulphur dioxide had ceased. The cooled solution was diluted with water, filtered from tar, and rendered alkaline with 4 N NaOH. The mixture was extracted with ether, and the ethanol extract was dried and treated with dry hydrogen chloride. o-*Trifluoromethylphenylhydrazine hydrochloride* was thereby obtained as a solid (5·3 g, 74%) which crystallized from water or methanol in colourless plates, m.p. 218° (decomp) (Found: C, 39·3; H, 3·9. $C_7H_8N_2F_3Cl$ requires: C, 39·5; H, 3·8%).

The *base* crystallized from light petroleum (b.p. 40–60°) in long colourless needles, m.p. 61–62° (Found: C, 48·2; H, 4·1; F, 32·1. $C_7H_7N_2F_3$ requires: C, 47·7; H, 4·0; F, 32·4%).

When the reduction of the diazonium salt was effected with stannous chloride the yield of *o*-trifluoromethylphenylhydrazine was 30%.

8-*Trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole*

A mixture of cyclohexanone (3 cc), *o*-trifluoromethylphenylhydrazine hydrochloride (3·5 g) and glacial acetic acid (10 cc) was maintained at 100° for 10 min. Dry hydrogen chloride was then passed through the mixture for 10 min, when it was cooled and poured into water (50 cc). The mixture was extracted with ether (2 × 50 cc), and the combined ethereal extracts were washed with 2 N Na_2CO_3 and dried. After removal of the solvents, the residue was fractionated to give 8-*trifluoromethyl*-1,2,3,4-*tetrahydrocarbazole* as a pale-yellow oil (3·0 g, 77%), b.p. 148–150°/2 mm. (Found: C, 65·0; H, 5·3; F, 23·3. $C_{13}H_{12}NF_3$ requires: C, 65·3; H, 5·0; F, 23·8%).

1-*Trifluoromethylcarbazole*

A suspension of sulphur (0·4 g) in a solution of the tetrahydrocarbazole (1·0 g) in quinoline (10 cc) was heated under reflux until no more hydrogen sulphide was evolved (ca. 45 min). The cooled mixture was poured on to a mixture of ice (50 g) and 2 N HCl (20 cc), and the whole was extracted several times with ether. The combined ethereal extracts were dried and distilled to give 1-*trifluoromethylcarbazole* (0·15 g) as a pale-yellow liquid b.p. 85–88°/0·1 mm, which set to a waxy solid, m.p. 49–50° (Found: C, 66·2; H, 3·7. $C_{13}H_8NF_3$ requires: C, 66·3; H, 3·5%). Light absorption λ_{max} 235, 262 and 295 mμ; log ε 3·49, 3·21, 3·14 respectively.

Acknowledgement—We thank Ciba Limited, Basle, for the award of a Scholarship (to R. T. W.).