[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SYRACUSE UNIVERSITY]

Condensation of Some Trifluoromethyl Ketones with Secondary Amines and Formaldehyde

G. F. GRILLOT,[1] SIEGFRIED AFTERGUT, SOLOMON MARMOR, AND FRED CARROCK

Received September 30, 1957

Condensation of trifluoroacetone with the methylols of piperidine, morpholine, and diisobutylamine produced the hydrates of 1,1,1-trifluoro-3-piperidinomethyl-4-piperidino-2-butanone, 1,1,1-trifluoro-3-morpholinomethyl-4-morpholino-2-butanone, and 1,1,1-trifluoro-3-di(isobutyl)aminomethyl-4-diisobutylamino-2-butanone, respectively.

1,1,1-Trifluoro-4-piperidino-2-butanol, was prepared by the reduction of *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine with sodium borohydride to *N*-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine, followed by the reduction of the latter by lithium aluminum hydride.

Trifluoromethyl ethyl ketone, trifluoromethyl *n*-butyl ketone, and *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine condense with piperidine and formaldehyde to form the hydrates of 1,1,1-trifluoro-3-piperidinomethyl-2-butanone, 1,1,1-trifluoro-3-piperidinomethyl-2-hexanone, and *N*-(α-trifluoroacetyl-β-piperidinopropionyl)piperidine, respectively.

The syntheses of some trifluoromethyl ketones of the structure $CF_3COCHRCH_2NR_2$ and the corresponding alcohols were attempted as starting materials for the future preparation of local anesthetics.

No reaction occurred between trifluoroacetone, paraformaldehyde, and the hydrochlorides of piperidine, morpholine, and diethylamine. Trifluoroacetone reacted with either formaldehyde and diethylamine, dimethylamine, di-*n*-propylamine and di-*n*-butylamine, or the methylols of these amines to form in each case an unstable oily product and an unstable amorphous solid. The structures of these products could not be determined, although all contained fluorine.

Trifluoroacetone and the methylols of piperidine, morpholine, and diisobutylamine gave in each case a single crystalline product which, on the basis of varied evidence, appears to be the hydrate of a product resulting from the substitution of two dialkylaminomethyl groups for two hydrogens on the methyl group of the trifluoroacetone molecule and can be assigned the following general structure.

$$CF_3C(OH)_2CH(CH_2NR_2)_2$$

Compound I, R_2N is piperidino, $C_5H_{10}N$—

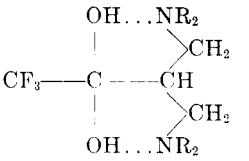
Compound II, R_2N is morpholino, OC_4H_8N—

Compound III, R_2N is diisobutylamino, $(C_4H_9)_2N$—

Acetone has previously been condensed with two moles each of dimethylamine and formaldehyde to form a corresponding but unhydrated product.[2]

After repeated attempts no product corresponding to a dialkylaminoethyl trifluoromethyl ketone could be isolated from the Mannich condensation.

Compounds I, II, and III gave indecisive chemical tests for the presence of the carbonyl group and this was attributed to internal hydrogen bonding as represented herewith:



Samples of compound I and II, prepared by the deposition of the crystals on the salt window from a chloroform solution, gave a strong infrared band at 3.03 microns corresponding to the absorption of associated hydroxyls.[3] No carbonyl absorption appeared in the infrared spectra of these two samples. If a sample of compound I was prepared by melting the sample on the salt window, the associated hydroxyl band disappeared and a carbonyl band appeared at 5.7 microns. It was concluded that the heating of compound I to its melting point served to remove a molecule of water, converting the carbonyl hydrate to the free ketone.

The preparation of 1,1,1-trifluoro-4-piperidino-2-butanol (IV) was eventually accomplished by the following series of reactions. Treatment of ethyl γ,γ,γ-trifluoroacetoacetate with piperidine gave *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V which was reduced to *N*-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine VI by means of sodium borohydride. Reduction of VI with lithium aluminum hydride afforded the amino alcohol IV.[4] The stepwise reduction of V to IV was undertaken because attempts to accomplish this reduction directly by

$$CF_3COCH_2CO_2C_2H_5 \xrightarrow{C_5H_{10}NH} CF_3COCH_2CONC_5H_{10} \xrightarrow{NaBH_4}$$
V

$$CF_3CHOHCH_2CONC_5H_{10} \xrightarrow{LiAlH_4} CF_3CHOHCH_2CH_2NC_5H_{10}$$
VI IV

(1) Inquiries should be addressed to this author.

(2) C. Mannich and O. Salzmann, *Ber.*, **72**, 506 (1939).

(3) H. M. Randall, R. G. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Company, Inc., New York, N. Y., 1949, p. 20.

(4) A number of tertiary amines prepared by the reduction of tertiary amides by lithium aluminum hydride are listed in Table VI of Chapter 10 of *Org. Reactions*, **VI**, Roger Adams, Editor in Chief, p. 505 (1951).

use of lithium aluminum hydride were unsuccessful. An alternate method for preparing VI was investigated by allowing ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate to react with piperidine. A small yield of the expected amide VI was realized, accompanied by the formation of the salt piperidinium β-hydroxy-γ,γ,γ-trifluorobutyrate, the structure of which was proven by its independent synthesis from β-hydroxy-γ,γ,γ-trifluorobutyric acid and piperidine.

Unlike *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine, (V),*N*-(acetoacetyl)piperidine was reduced successfully to 4-*N*-piperidino-2-butanol by lithium aluminum hydride. The hydrochloride and the benzoate hydrochloride of the resulting amino alcohol were proved to be identical with these derivatives of the amino alcohol obtained by Mannich and Hof[5] by reducing the condensation product of acetone, formaldehyde, and piperidine.

The reaction of formaldehyde and piperidine with trifluoromethyl ethyl ketone, trifluoromethyl *n*-butyl ketone, and *N*-(γ,γ,γ-trifluoroacetoacetyl)-piperidine V gave the expected hydrated Mannich bases VII. These substances are apparently *gem*

$$CF_3COCHRCH_2NC_5H_{10}\cdot H_2O$$
VII

diols with a structure similar to that proposed for the hydrated "disubstituted" Mannich bases obtained from trifluoroacetone. The assignment of *gem*-diol structures to these hydrates receives support from their failure to undergo carbonyl reactions under the usual conditions. The Mannich base derived from V, *N*-(α-trifluoroacetyl-β-piperidinopropionyl) piperidine [VII, R=CON(C_5H_{10})] exhibited low stability. An attempt to recrystallize it from boiling aqueous methanol caused its decomposition to *N*-(α-trifluoroacetylacryloyl)piperidine hydrate VIII. The structure of the latter was confirmed by its synthesis from *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V and formaldehyde in the presence of sodium hydroxide.

$$\text{VII } (R = CONC_5H_{10}) \longrightarrow CF_3COC(=CH_2)CONC_5H_{10}\cdot H_2O$$
VIII

$$CF_3COCH_2CONC_5H_{10} + CH_2O$$
V

(↑NaOH)

1,1,1-Trifluoromethyl-3-piperidinomethyl-2-butanone hydrate (Compound VII, R=CH_3) was reduced by sodium borohydride to 1,1,1-trifluoromethyl-3-piperidinomethyl-2-butanol (Compound IX) which was then converted to the hydrochloride of its *p*-nitrobenzoate ester. Reduction of 1,1,1-trifluoromethyl-3-piperidinomethyl-2-hexanone hydrate (Compound VII, R = *n*-propyl) with sodium borohydride produced 1,1,1-trifluoromethyl-3-piperidinomethyl-2-hexanol (Compound X). The latter was also obtained as the *p*-aminobenzoate ester and as the hydrochloride of this ester.

(5) C. Mannich and W. Hof, *Arch. Pharm.*, **265**, 589 (1927).

EXPERIMENTAL[6]

1,1,1-Trifluoro-3-piperidinomethyl-4-piperidino-2,2-butanediol (Compound I). One-tenth mole of *N*-methylolpiperidine was prepared by adding 8.5 ml. of cold 37% aqueous formaldehyde solution to 8.5 g. (0.1 mole) of piperidine in 17 ml. of water and maintaining the mixture at 0° for 1 hr. Then 11 g. (0.1 mole) of trifluoroacetone[7] was added to the resulting *N*-methylolpiperidine with cooling by a Dry Ice–Cellosolve bath. The reaction flask was fitted with a Dry Ice reflux condenser and the cooling bath was removed. The flask was permitted to stand (with occasional shaking) at room temperature for about 30 min. A heavy precipitate formed which was twice recrystallized from acetone, m.p. 93–95°. A yield of 15.5 g. (48%) was obtained.

Anal. Calcd. for $C_{15}H_{27}F_3N_2O_2$: C, 55.7; H, 8.34; N, 8.64; mol. wt., 324; neut. equiv., 162. Found: C, 55.5; 55.6; H, 8.14, 8.46; N, 8.15; 8.44; mol. wt. (cryoscopic, benzene), 352, 350; neut. equiv., 167.4, 166.

If this diol is treated with 2,4-dinitrophenylhydrazine hydrochloride in methanol, followed by addition of methanolic KOH, a slight muddy red color appeared. If a blank test was run a greenish black color appeared which faded rapidly, while acetone gave a deep red color.

A determination of the number of active hydrogens in this diol by means of the Zerewitinoff test indicated 2^+ per mol.

Further, when this diol was esterified using the Schotten-Baumann technique a small amount of a viscous product, insufficient to characterize, was obtained. This product did give a positive hydroxamic acid test which is indicative of an ester.

1,1,1-Trifluoro-3-morpholinomethyl-4-morpholino-2,2-butanediol (Compound II). This compound was prepared in the same fashion as compound I above by substituting *N*-methylolmorpholine for the *N*-methylolpiperidine. The resulting crude product was twice recrystallized from methyl ethyl ketone, m.p. 83.5–87°. A yield of 13 g. (36%) was obtained.

Anal. Calcd. for $C_{13}H_{23}F_3N_2O_4$: C, 47.6; H, 7.03; N, 8.55. Found: C, 47.7; H, 7.6; N, 8.55.

1,1,1-Trifluoro-3-di(isobutyl)aminomethyl-4-diisobutylamino-2,2-butanediol (Compound III). This compound was prepared in the same fashion as compound I above by substituting the methylol of diisobutylamine for the *N*-methylolpiperidine. The crude product was obtained as an oil which crystallized on standing. The latter was recrystallized twice from acetone and melted at 79–81°. The yield was 8 g. (20%).

Anal. Calcd. for $C_{21}H_{43}F_3N_2O_2$: C, 61.9; H, 10.55; N, 6.55. Found: C, 61.3; H, 10.44; N, 6.8.

N-(γ,γ,γ-trifluoroacetoacetyl)piperidine (V). The apparatus used was similar to that described for the preparation of benzoylacetanilide.[8] A boiling mixture of 184 g. (1 mole) of ethyl γ,γ,γ-trifluoroacetoacetate[9] in 200 ml. of dry xylene was treated with 76.5 g. (0.9 mole) of dry piperidine, added dropwise, and the reaction mixture was refluxed for 30 min. Vacuum concentration and fractionation gave 147 g. (73%) of yellow oil, b.p. 119–120°/7 mm. (n_D^{27} 1.4647, which solid-

(6) Microanalyses for C, H, and N by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(7) A. L. Henne and R. L. Pelley, *J. Am. Chem. Soc.*, **74**, 1428 (1952).

(8) C. J. Kibler and A. Weissberger, *Org. Syntheses*, **Coll. Vol. III**, 108 (1955).

(9) A. L. Henne, M. S. Newman, L. L. Quill, and R. A. Staniforth, *J. Am. Chem. Soc.*, **69**, 1819 (1947).

ified on cooling. After recrystallization from petroleum ether (b.p. 30–60°) it had m.p. 27.4–30.0° (corr.)

Anal. Calcd. for $C_9H_{12}F_3NO_2$: C, 48.43; H, 5.42. Found: C, 48.23; H, 6.07.

The *2,4-dinitrophenylhydrazone* was recrystallized from aqueous methanol, m.p. 114.5–115.5° (corr.).

Anal. Calcd. for $C_{15}H_{16}F_3N_5O_5$: C, 44.67; H, 3.99. Found: C, 45.13; H, 3.94.

The *copper chelate* was recrystallized from aqueous methanol, m.p. 207.0–207.5° (corr.).

Anal. Calcd. for $C_{18}H_{22}CuF_6N_2O_4$: Cu, 12.5. Found: Cu, 12.6.

N-(β-hydroxy-γ,γ,γ-trifluorobutyryl)piperidine (VI). To a stirred solution of 44.6 g. (0.2 mole) of V in 200 ml. of ether was added, in small portions and with cooling, 4 g. (0.1 mole) of sodium borohydride, after which stirring at room temperature was continued for 1.5 hr. Unreacted borohydride was removed by filtration, and the filtrate was treated with 20 ml. of 5% HCl with stirring at room temperature for 1.5 hr., then freed of solids by filtration. The organic layer was washed, dried, and concentrated, giving 36 g. (79%) of product. The analytical sample, recrystallized from benzene–petroleum ether, had m.p. of 109.4–109.8° (corr.).

Anal. Calcd. for $C_9H_{14}F_3NO_2$: C, 48.00; H, 6.27. Found: C, 47.89; H, 6.58.

1,1,1-Trifluoro-4-piperidino-2-butanol (IV). A solution of 31.5 g. (0.14 mole) of VI in 100 ml. of dry tetrahydrofuran was added to 8.7 g. (0.24 mole) of lithium aluminum hydride in 200 ml. of ether. The product was isolated according to the procedure of Micovic and Mihailovic[10] and fractionated to give 19 g. (64%) of material, b.p., 94° (14 mm.), n_D^{24} 1.4232, d_4^{24} 1.151.

Anal. Calcd. for $C_9H_{16}F_3NO$: C, 51.18; H, 7.64; M.R., 46.43; neut. equiv. 211.2. Found: C, 51.19; H, 8.39; M.R., 46.73; neut. equiv. 211.2.

The *phenylurethan* was recrystallized from petroleum ether, m.p. 93.0–93.6° (corr.).

Anal. Calcd. for $C_{16}H_{21}F_3N_2O_2$: C, 58.17; H, 6.41. Found: C, 58.56; H, 6.76.

The *methyl p-toluenesulfonate* was recrystallized from ethyl acetate–methanol, m.p. 122.8–124.0° (corr.).

Anal. Calcd. for $C_{17}H_{26}F_3NO_4S$: C, 51.37; H, 6.59. Found: C, 51.88; H, 7.03.

The *p-nitrobenzoate hydrochloride* was recrystallized from acetone-methanol, m.p. 191–193° (corr.).

Anal. Calcd. for $C_{16}H_{19}F_3N_2O_4$·HCl: Cl, 8.94. Found: Cl, 8.87.

The *p-aminobenzoate* was prepared from the latter by hydrogenation using PtO_2 as catalyst, followed by neutralization with concd. NH_4OH. After recrystallization from aqueous methanol, it had m.p. 103.0–103.8° (corr.).

Anal. Calcd. for $C_{16}H_{21}F_3N_2O_2$: C, 58.13; H, 6.41; neut. equiv., 165. Found: C, 59.05; H, 6.81; neut. equiv., 167.

Ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate. This ester has been previously prepared by other methods.[11,12] The reduction was performed in a manner similar to that described for the preparation of VI by treating a solution of 49 g. (0.26 mole) of ethyl γ,γ,γ-trifluoroacetoacetate in 50 ml. of ether with 3.8 g. (0.1 mole) of sodium borohydride. Fractionation afforded 34 g. (69%) of product, b.p. 80–83° (14–15 mm.), n_D^{25} 1.3732 (reported[12] b.p. 81–83°/15 mm., n_D^{25} 1.3720).

The *phenylurethan*, melted at 67–69° (reported[12] m.p. 70.0–70.5°).

Reaction of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate with piperidine. A boiling solution 49.5 g. (0.22 mole) of ethyl β-hydroxy-γ,γ,γ-trifluorobutyrate in 75 ml. of dry xylene was treated with 27 g. (0.32 mole) of dry piperidine. The mixture was refluxed for 2 hr., decolorized with Nuchar and vacuum concentrated, producing 20 g. of crude solid product which was isolated by filtration. This product was extracted with water. The water insoluble fraction was recrystallized from benzene and gave 3.6 g. of VI. The aqueous extract was treated with benzene to remove traces of VI, evaporated to near dryness at reduced pressure and dried by azeotropic distillation with benzene, giving 12 g. of piperidinium β-hydroxy-γ,γ,γ-trifluorobutyrate which, after recrystallization from benzene, had m.p. 100.8–101.8° (corr.).

Anal. Calcd. for $C_9H_{16}F_3NO_3$: C, 44.44; H, 6.63; neut. equiv., 243. Found: C, 44.46; H, 6.62; neut. equiv., 243.

The melting point of this salt was not depressed by admixture of the compound obtained by treatment of β-hydroxy-γ,γ,γ-trifluorobutyric acid[12] with piperidine.

4-(N-piperidino)-2-butanol. *N*-(acetoacetyl)piperidine[13] was first prepared by the following procedure:

A solution of 65 g. (0.5 mole) of acetoacetic ester in 70 ml. of xylene was heated to 145°. To this solution was added 34 g. (0.4 mole) of piperidine in small portions. Heating was continued for 45 min. and after vacuum fractionation 55 g. (88%) of product was collected, b.p., 126–128° (4 mm.).

This product was reduced by the method of Uffer and Schlitter[14]:

A one-liter three-necked flask equipped with a dropping funnel, mercury sealed stirrer, and a Y tube fitted with a reflux condenser was charged with 500 ml. of dry ether and was swept out with dry nitrogen. Twenty-five grams (0.66 mole) of lithium aluminum hydride was added while the flow of nitrogen was maintained. Then a solution of 59 g. (0.35 mole) of *N*-(acetoacetyl)piperidine in 50 ml. of dry ether was admitted to the reaction mixture during a period of 1 hr. The reaction mixture was stirred for 30 min. after the last of the ketoamide was added, and then was refluxed for 24 hr. On cooling, water was added very cautiously and the mixture was stirred and allowed to stand at room temperature to ensure complete decomposition of the excess hydride. To the resulting slurry, 10% sulfuric acid was added until all the white precipitate dissolved. The acid solution was separated from the ether and the latter was extracted once with 50 ml. of 10% sulfuric acid. The combined acid solutions were then made strongly alkaline with 10*N* sodium hydroxide and extracted twice with 100-ml. portions of ether. The ether extracts were dried over anhydrous $MgSO_4$ and distilled. A total of 25 g. (45% of theory) of product boiling at 103° (11 mm.) was obtained.

The hydrochloride of the resulting amino alcohol was prepared and was recrystallized from alcohol and acetone, m.p., 145°. The benzoate hydrochloride, recrystallized from acetone, melted at 192°. Mixed melting point determinations were run with each derivative, using the hydrochloride and the benzoate ester hydrochloride prepared from an authentic sample of 4-(*N*-piperidino)-2-butanol prepared by the method of Mannich and Hof.[5] In neither case was any depression of the melting point observed.

1,1,1-Trifluoro-3-piperidinomethyl-2-butanone hydrate (VII R = CH_3). Trifluoromethyl ethyl ketone[15] (12.6 g., 0.1 mole) was treated with 8.5 g. (0.1 mole) of piperidine and 10 ml. of 37% formalin with cooling. Addition of water and chilling produced 21 g. (87%) of product which was recrystallized from aqueous ethanol and had m.p. 98–100°.

Anal. Calcd. for $C_{10}H_{16}F_3NO\cdot H_2O$: C, 49.78; H, 7.52. Found: C, 50.12; H, 8.45.

The *picrate*, recrystallized from aqueous methanol, had m.p. 105–107°.

(10) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(11) H. M. Walborski and M. Schwarz, *J. Am. Chem. Soc.*, **75**, 3241 (1953).

(12) E. T. McBee, O. R. Pierce, and D. D. Smith, *J. Am. Chem. Soc.*, **76**, 3722 (1954).

(13) P. W. Vittum, K. P. Griffin, and A. Weissberger, U. S. Patent **2,378,266**; *Chem. Abstr.*, **39**, 3743 (1945).

(14) A. Uffer and E. Schlitter, *Helv. Chim. Acta*, **31**, 1397 (1948).

(15) A. Sykes, J. C. Tatlow, and C. R. Thomas, *Chem. & Ind. (London)*, 630 (1955).

Anal. Calcd. for $C_{16}H_{19}F_3N_4O_8 \cdot H_2O$: C, 40.85; H, 4.50. Found: C, 41.44; H, 5.26.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanone hydrate (VII, R = *n*-propyl). Trifluoromethyl *n*-butyl ketone[16] (15.4 g., 0.1 mole) was treated with 8.5 g. (0.1 mole) of piperidine and 10 ml. of 37% formalin, yielding 23 g. (85%) of product. After recrystallization from aqueous methanol it melted at 82–84°.

Anal. Calcd. for $C_{12}H_{20}F_3NO \cdot H_2O$: C, 53.55; H, 8.24. Found: C, 54.09; H, 8.74.

The *picrate*, recrystallized from aqueous methanol, had m.p. 93–95°.

Anal. Calcd. for $C_{18}H_{23}F_3N_4O_8 \cdot H_2O$: C, 43.37; H, 5.06. Found: C, 43.81; H, 5.53.

N-(α-trifluoroacetyl-β-piperidinopropionyl)piperidine hydrate (VII, R = $CON(C_5H_{10})$). A solution of 5 g. (0.22 mole) of N-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 20 ml. of 95% ethanol was cooled to 10° and treated with 1.9 g. (0.22 mole) of piperidine and 2.2 g. (0.22 mole) of 30% formalin with cooling and shaking. There was obtained 6.8 g. (90%) of product which, after recrystallization from ether–petroleum ether (b.p. 30–60°), had m.p. 96–98°.

Anal. Calcd. for $C_{15}H_{23}F_3N_2O_2 \cdot H_2O$: C, 53.25; H, 7.45; neut. equiv., 338. Found: C, 53.35; H, 7.39; neut. equiv., 339.

The *picrate*, after washing with ether, had m.p. 92–93°.

Anal. Calcd. for $C_{21}H_{26}F_3N_5O_9 \cdot H_2O$: C, 44.44; H, 4.97; neut. equiv., 567. Found C, 44.41; H, 4.96; neut. equiv., 566.

An attempt to recrystallize the Mannich base from hot aqueous methanol caused its decomposition to VIII.

N-(α-trifluoroacetylacryloyl)piperidine hydrate (VIII). A solution of 5 g. (0.22 mole) of *N*-(γ,γ,γ-trifluoroacetoacetyl)piperidine V in 15 ml. of methanol, to which ten drops of 15% NaOH had been added, was cooled to 20° and treated with 3 g. (0.03 mole) of 30% formalin, added dropwise with vigorous shaking. After heating the mixture to 50° and shaking vigorously for 5 min., 5 ml. of water was added and the mixture was cooled, affording 4 g. (70%) of product which was recrystallized from aqueous methanol, m.p. 138.4–140.0°.

Anal. Calcd. for $C_{10}H_{12}F_3NO_2 \cdot H_2O$: C, 47.43; H, 5.57. Found: C, 48.05; H, 5.38.

1,1,1-Trifluoro-3-piperidinomethyl-2-butanol (IX). To a solution of 5 g. (0.023 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-butanone hydrate (compound VII, R = CH_3) in 100 ml. of ether was added in small portions 0.38 g. (0.01 mole) of sodium borohydride. Stirring was continued for 1.5 hr. Unreacted borohydride was removed by filtration and the filtrate was treated with a solution of 2 g. of sodium hydroxide in 50 ml. of water and the mixture was stirred vigorously for 1 hr. The water layer was separated and extracted with ether and the combined ether extracts were dried over magnesium sulfate. Upon distillation of the ether extracts 2.5 g. (50%) of a colorless oily liquid, b.p. 79–81° (4 mm.), was obtained.

p-Nitrobenzoate hydrochloride. Recrystallized from a chloroform–petroleum ether solution, m.p. 206–208° (corr.).

Anal. Calcd. for $C_{17}H_{22}O_4F_3N_2Cl$: C, 49.69%; H, 5.39%. Found: C, 49.51%; H, 6.18%.

1,1,1-Trifluoro-3-piperidinomethyl-2-hexanol (X). A procedure was employed similar to that described above for the preparation of 1,1,1-trifluoro-3-piperidinomethyl-2-butanol (IX). When 10 g. (0.037 mole) of 1,1,1-trifluoro-3-piperidinomethyl-2-hexanol hydrate (Compound VII R = *n*-propyl) was reduced, a colorless oily liquid was obtained. B.p. 92–95° (4 mm.). Yield 4.7 g. (47%).

p-Aminobenzoate. Repeated attempts to purify the *p*-nitrobenzoate derivative of the above alcohol by recrystallization failed. Seven grams (0.016 mole) of the crude *p*-nitrobenzoate hydrochloride in 100 ml. of ethyl alcohol was reduced using 150 mg. of Adams' platinum catalyst and 0.048 mole of hydrogen. After reduction was complete the catalyst was removed by filtration. After many repeated attempts at crystallization of the *p*-aminobenzoate hydrochloride had failed, an alcohol solution of this ester hydrochloride was neutralized with sodium hydroxide, whereupon the color of the solution changed from yellow to a deep orange brown. Upon addition of water a nearly colorless precipitate formed. This was recrystallized from an aqueous alcohol solution and melted at 92–94°. Yield 3.8 g. (63%).

Anal. Calcd. for $C_{19}H_{27}F_3N_2O_2$: C, 61.27%; H, 7.31%. Found: C, 61.42%; H, 7.82%.

p-Aminobenzoate hydrochloride. To 1.4 g. (0.0035 mole) of the free ester was added exactly 37.8 ml. of 0.0924*N* HCl. A white precipitate remained which was washed several times with water and was then dried. It melted at 223–225° (corr.).

Anal. Calcd. for $C_{19}H_{28}F_3N_2O_2Cl$: C, 55.81%; H, 6.89%. Found: C, 55.91%; H, 7.29%.

Acknowledgment. We extend our thanks to Dr. W. C. Fernelius of Pennsylvania State University for suggesting this problem and to Samuel P. Sadtler and Sons, Inc., Philadelphia, who prepared and assisted us in interpreting the infrared spectra.

SYRACUSE 10, N. Y.

(16) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Preparation of Some Substituted α,β-Diphenylacrylic Acids and Related Derivatives

B. H. ALEXANDER AND W. F. BARTHEL

Received September 26, 1957

The preparation of a number of compounds related to ethyl β-(3,4-methylenedioxyphenyl)-α-phenylacrylate is described.

A part of the insecticide research program under way in this laboratory is concerned with the synthesis of insect toxicants, synergists, repellents, and attractants. The search for these compounds originally was conducted on an empirical basis, for no relationship between chemical constitution and biological activity was known. However, with the synthesis of many compounds and their subsequent