yielded, respectively, the crystalline N-acetyl and N-benzoyl derivatives.

Experimental

N-Acetyl-L-tyrosine Methyl Ester.—Fifteen grams of the methyl ester[2] of L-tyrosine was acetylated by Fischer's[3] method with mechanical stirring and the use of 7.6 g. of acetyl chloride, 800 cc. of absolute chloroform, 9 g. of anhydrous sodium carbonate and 60 cc. of water. At the end of the reaction the suspended solid was collected on a filter, washed with chloroform and extracted with 400 cc. of hot ethyl acetate in several portions. The ethyl acetate solution upon concentration deposited in two crops 16.6 g. or 91% of nearly pure product. The chloroform solution yielded a small amount of product. The compound was purified by recrystallization from ethyl acetate as colorless, rod-shaped prisms which, after being dried overnight in an evacuated desiccator over calcium chloride, were usually in a solvated state and melted at 118–120°. Sometimes the crystals were almost solvent-free and melted near 135°. Drying at 100° *in vacuo* yielded solvent-free crystals; m.p. 136–137° (uncor.); $[\alpha]^{20}D$ +29.7° in methanol (*c* 0.41).

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.91. Found: C, 60.56; H, 6.38; N, 5.88.

O-*p*-Toluenesulfonyl-N-acetyl-L-tyrosine Methyl Ester.—A solution of 8.8 g. of methyl ester of N-acetyl-L-tyrosine and 7.4 g. of *p*-toluenesulfonyl chloride in 185 cc. of acetone, after being mixed with 37 cc. of *N* sodium hydroxide solution, was refluxed for one hour and then concentrated at 25° *in vacuo* to 50 cc. The sirupy product was separated from the aqueous solution, which was extracted thoroughly with chloroform. The sirup was combined with the chloroform extract; the solution was extracted with 10% sodium carbonate solution, washed with water and dried over sodium sulfate. After removal of the solvent *in vacuo*, the thick sirup was crystallized as colorless needles from ethyl acetate–petroleum ether (b.p. 30–75°); yield 10.4 g. or 72%; m.p. 90–91° (cor.); $[\alpha]^{20}D$ +15.5° in methanol (*c* 0.8). Samples for analysis and rotation were dried in an evacuated desiccator over calcium chloride.

Anal. Calcd. for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; S, 8.19. Found: C, 58.36; H, 5.38; N, 3.59; S, 8.11.

O-*p*-Toluenesulfonyl-L-tyrosine.—A solution of 5.7 g. of pure methyl ester of O-*p*-toluenesulfonyl-N-acetyl-L-tyrosine in a mixture of 100 cc. of glacial acetic acid and 100 cc. of 38% hydrochloric acid was refluxed for two hours. The solution was cooled, mixed with 850 cc. of water and neutralized to litmus paper with ammonium hydroxide. The precipitated crystals were collected on a filter and washed with water; air-dried; yield 4.7 g. Recrystallized from water as colorless needles and dried at 79° *in vacuo*, it melted at 213–214° (uncor., dec.); $[\alpha]^{20}D$ +9.0° in *N* hydrochloric acid (*c* 0.42) or +9.5° (*c*, 3.16).

Anal. Calcd. for $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18; S, 9.56. Found: C, 57.02; H, 5.13; N, 4.14; S, 9.49.

O-*p*-Toluenesulfonyl-N-acetyl-L-tyrosine.—The acetylation of 2.3 g. of O-*p*-toluenesulfonyl-L-tyrosine was carried out according to Fischer,[3] using 0.7 g. of acetyl chloride, 100 cc. of absolute chloroform, 1.2 g. of anhydrous sodium carbonate and 8 cc. of water. The solvent was removed at 25–30° *in vacuo*. A filtered solution of the residual oil in 20 cc. of water was made slightly acid (litmus paper) by addition of hydrochloric acid which precipitated 0.8 g. of starting compound. The addition of more acid to the filtrate precipitated a sirup. The decanted aqueous layer was extracted with two 10-cc. portions of ethyl acetate which, after being combined with an ethyl acetate solution of the sirup, deposited at 25° 0.1 g. of starting compound. After removal of the solvent at 25° the sirup was stirred with 2% hydrochloric acid to yield 1.2 g. of crystals. The compound crystallized, slowly the first time, as rosettes of colorless short blades from its solution in ethyl acetate–petroleum ether; m.p. 134–135° (uncor.); $[\alpha]^{20}D$ +29.4° in methanol (*c* 0.83).

Anal. Calcd. for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71; S, 8.50. Found: C, 57.38; H, 5.00; N, 3.79; S, 8.31.

(2) E. Fischer and W. Schrauth, *Ann.*, **354**, 34 (1907).

(3) E. Fischer, *Ber.*, **37**, 2495 (1904).

O-*p*-Toluenesulfonyl-N-benzoyl-L-tyrosine.—O-*p*-Toluenesulfonyl-L-tyrosine (1.5 g.) was benzoylated by the method of Fischer,[4] using 1.9 g. of benzoyl chloride, 3 g. of sodium bicarbonate and 40 cc. of water. After the crystalline product had been extracted thoroughly with petroleum ether, it was recrystallized as colorless, hexagonal plates from acetone–petroleum ether; yield 0.9 g.; m.p. 194–195° (uncor.); $[\alpha]^{20}D$ −1.3° (*c* 2.61) in water containing 1.1 molecular equivalents of sodium hydroxide.

Anal. Calcd. for $C_{23}H_{21}NO_6S$: C, 62.85; H, 4.82; N, 3.19; S, 7.30. Found: C, 63.02; H, 5.10; N, 3.12; S, 7.39.

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(4) E. Fischer, *ibid.*, **32**, 2454 (1899).

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Some N-(β-Substituted Ethyl)-N,N-dibenzylamines

BY IRVING ALLAN KAYE AND HERMAN HORN

The importance of the dibenzylamino residue as a contributor to the activity of Dibenamine[1] [N-(2-chloroethyl)-dibenzylamine] hydrochloride, a compound commercially available as a potent and specific adrenergic blocking agent,[2] suggested the preparation of several N,N-dibenzyl-N′-aralkyl-N′-heterocyclic-ethylenediamines for pharmacological screening tests. The products, structurally related to several histamine antagonists on the market,[3] were prepared by alkylating an N-aralkyl-N-heterocyclicamine with 2-dibenzylaminoethyl chloride hydrochloride in the presence of lithium amide. The benzohydryl ether of 2-dibenzylaminoethanol (an analog of Benadryl[4]),

$$R{-}NH{-}CH_2R' + LiNH_2 + (C_6H_5CH_2)_2NCH_2CH_2Cl\cdot HCl \longrightarrow R{-}N(CH_2R'){-}CH_2CH_2N(CH_2C_6H_5)_2$$

R = 2-pyridyl, 2-pyrimidyl, 2-thiazolyl, or 2-lepidyl

R′ = phenyl, *p*-methoxyphenyl or *p*-chlorophenyl

also synthesized, was obtained by heating the benzohydryl ether of ethylene chlorohydrin with dibenzylamine.

$$(C_6H_5)_2CHOCH_2CH_2Cl + 2(C_6H_5CH_2)_2NH \longrightarrow (C_6H_5)_2CHO{-}CH_2CH_2N(CH_2C_6H_5)_2 + (C_6H_5CH_2)_2NH\cdot HCl$$

Three of the products, N,N-dibenzyl-N′-(benzyl and *p*-chlorobenzyl)-N′-(2-pyridyl)-ethylenediamines and N,N-dibenzyl-N′-benzyl-N′-(2-thiazolyl)-ethylenediamine, tested against histamine using the isolated guinea pig ileum strip, showed less than 0.1% of the activity of Pyribenzamine.[5a,6] None of these compounds showed any evidence of

(1) Trademark of Smith, Kline and French Laboratories.

(2) W. S. Gump and E. J. Nikawitz, THIS JOURNAL, **72**, 1309 (1950); J. F. Kerwin, T. F. Herdegen, R. Y. Heisler and G. E. Ullyot, *ibid.*, **72**, 940 (1950).

(3) B. Idson, *Chem. Revs.*, **47**, 377 (1950).

(4) Trademark of Parke Davis & Co.

(5) The authors wish to thank (a) Dr. Harold Blumberg and Mr. Eric Meyer of Endo Products, Inc., and (b) Dr. C. Chester Stock of The Sloan-Kettering Institute for Cancer Research for this information.

(6) "Pyribenzamine" is the trademark of Ciba Pharmaceutical Products, Inc., for N,N-dimethyl-N′-benzyl-N′-(2-pyridyl)-ethylenediamine.

TABLE I

N,N-DIBENZYL-N'-ARALKYL-N'-SUBSTITUTED ETHYLENEDIAMINES $RN(CH_2R')CH_2CH_2N(CH_2C_6H_5)_2$

R[a]	R	B.p., °C.	B.p., Mm.	Yield, %	$n^{25}D$	Nitrogen, % Formula	Calcd.	Found
C_5H_4N	C_6H_5	200–204	0.05	95	1.6082	$C_{28}H_{29}N_3$	10.33	10.47
C_5H_4N	$C_6H_5(OCH_3)(4)$[b]	234–236	.10	76	1.6059	$C_{29}H_{31}N_3O$	9.60	9.55
C_5H_4N	$C_6H_4Cl(4)$[c]	212–213	.08	78	1.6118	$C_{28}H_{28}ClN_3$	9.51	9.45
$C_4H_3N_2$	$C_6H_4(OCH_3)(4)$	210–212	.01	27	1.6021	$C_{28}H_{30}N_4O$	12.77	12.79
$C_{10}H_8N$	$C_6H_5Cl(4)$	164–165.5[d]		83		$C_{33}H_{32}ClN_3 \cdot 2HCl$	7.26	7.15
C_3H_2NS	C_6H_5	216–219	0.05	68	1.6100	$C_{26}H_{27}N_3S$	10.16	9.93

[a] C_5H_4N, $C_4H_3N_2$, $C_{10}H_8N$, C_3H_2NS are 2-pyridyl, 2-pyrimidyl, 2-lepidyl and 2-thiazolyl, respectively. [b] The picrate melted at 119.5–120° after two recrystallizations from methanol. Calcd. for $C_{29}H_{31}N_3O \cdot 2C_6H_3N_3O_7$: N, 12.61. Found: N, 12.20. [c] The picrate, recrystallized twice from methanol, melted at 149–150°. *Anal.* Calcd. for $C_{28}H_{28}ClN_3 \cdot 2C_6H_3N_3O_7$: N, 14.01. Found: N, 13.80. [d] Melting point of dihydrochloride after three recrystallizations from isopropyl alcohol.

ability to retard the growth of sarcoma 180 in mice.[5b]

Experimental[7]

Intermediates.—2-Dibenzylaminoethyl chloride hydrochloride, prepared in 85% yield by the procedure of Gump and Nikawitz,[8] melted at 187–189° after one recrystallization from isopropyl alcohol. Although this is below the reported melting point (194–195°), the product gave a satisfactory analysis (Calcd. for $C_{16}H_{19}Cl_2N$: Cl, 23.94. Found: Cl, 24.00) and was used successfully in the condensation reactions. The 2-(benzyl, *p*-methoxybenzyl and *p*-chlorobenzyl) - aminopyridines,[8] 2 - (*p* - methoxybenzyl)-aminopyrimidine,[8] 2-(*p*-chlorobenzyl)-aminolepidine[9] and 2-benzylaminothiazole[10] were described in other publications.

Benzohydryl Ether of 2-Dibenzylaminoethanol.—A mixture of 24.7 g. (0.1 mole) of the benzohydryl ether of ethylenechlorohydrin[11] and 39.4 g. (0.2 mole) of dibenzylamine was heated at a bath temperature of 150–155° for 36 hours. Ether was added to the cooled melt and the dibenzylamine hydrochloride was removed by filtration and washed well with ether. To the filtrate was added ethereal hydrogen chloride to maximum precipitation. The crude salt was separated by filtration and washed with ether. After air-drying, it weighed 31.2 g. (71%) and melted at 185–187°. After two recrystallizations from acetone, the melting point remained constant at 186–187°.

Anal. Calcd. for $C_{29}H_{29}NO \cdot HCl$: N, 3.16; Cl, 7.99. Found: N, 3.10; Cl, 7.78.

N,N-Dibenzyl-N'-aralkyl-N'-(2-pyridyl, 2-Pyrimidyl, 2-Lepidyl and 2-Thiazolyl)-ethylenediamines.—A mixture of 0.05 mole of the secondary amine, 17.8 g. (0.06 mole) of 2-dibenzylaminoethyl chloride hydrochloride, 3.1 g. (0.12 mole) of 90% lithium amide and 100 ml. of benzene (previously dried over calcium hydride) was refluxed for 24 hours. The reaction mixture was filtered while still hot and the insoluble material washed well with benzene. After removing the solvent from the filtrate, the oil which remained was distilled *in vacuo*.

In the condensation with 2-(*p*-methoxybenzyl)-aminopyrimidine by this method, about one-half of the reactants were recovered and a non-distillable substance obtained. Modifying the procedure by adding the 2-dibenzylaminoethyl chloride hydrochloride to a mixture of lithium amide, the 2-pyrimidylamine and benzene, which had been refluxed for 24 hours, and refluxing for an additional 24 hours, gave the desired product in low yield.

N,N-Dibenzyl-N'-(*p*-chlorobenzyl)-N'-(2-lepidyl)-ethylenediamine was isolated and purified as its water-insoluble hydrochloride. The remaining products failed to form crystalline salts other than picrates, which were prepared from two of the bases. Results are summarized in Table I.

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(7) Melting points are corrected; boiling points are not.
(8) I. A. Kaye and I. C. Kogon, *Rec. trav. chim.*, in press.
(9) I. A. Kaye, THIS JOURNAL, **71**, 2322 (1949).
(10) I. A. Kaye and C. L. Parris, *ibid.*, in press.
(11) I. A. Kaye, *ibid.*, **73**, 5468 (1951).

A Convenient Method for Fluorinating Certain Chlorocarbons with Antimony Trifluoride

BY H. DEAN MALLORY

A number of methods are available for fluorinating chlorocarbons through the use of anhydrous hydrogen fluoride or elementary fluorine at some stage in the process; however, the amount of equipment necessary to handle these compounds is sometimes prohibitive in the small laboratory. The process described in this note requires no special apparatus, and when applicable is capable of yielding high purity fluorocarbons. It was developed specifically for the preparation of methylfluoroform[1] from methylchloroform although it is well adapted to the preparation of difluorodichloromethane from carbon tetrachloride, or difluorochloromethane from chloroform. Large scale production of the latter two compounds has been reported[2] by Booth and Bixby using the same starting materials as used here although the procedures differ. This process is applicable if the final product is: (a) gaseous at room temperature or slightly above and (b) the most highly fluorinated compound obtainable with antimony trifluoride. The final product will contain on the order of 95% of the highest fluoride. An exception is noted with ethylidene fluoride; it is easily formed from CH_3CHCl_2 but is then quickly decomposed to tar by the fluorinating mixture and the yields approach zero after three seconds contact. This process will give 25% yields[3] of CH_3CHF_2 if the reaction gases are collected after the first stage but no CH_3CHClF was ever isolated. Whalley[4] has obtained 40% yields of the monofluoride with a $HF–SnCl_4$ process.

Experimental Details

The apparatus is shown in Fig. 1 and consists of a flask with a separatory funnel for adding antimony pentachloride, a water jacketed glass column reactor, sodium hydroxide scrubber, drying tube and a Dry Ice–acetone trap. The initial reaction between chlorocarbon and SbF_3 catalyzed by a few drops of $SbCl_5$, occurs in the flask containing the calculated amount of reactants. The gas products from this stage consist of materials boiling near room temperature but which are incompletely reacted; the amount of ultimate product present may be 30% or less. Flow of gas from the flask to the column reactor is controlled by adding $SbCl_5$

(1) Reported in the author's Ph.D. thesis, The State University of Iowa, Iowa City, Iowa, February, 1950.
(2) A. S. Booth and E. May Bixby, *Ind. Eng. Chem.*, **24**, 637 (1932).
(3) About that reported for a similar process by Albert L. Henne and Mary W. Renoll, THIS JOURNAL, **58**, 889 (1936).
(4) Wm. B. Whalley (to Imperial Chemical Industries, Ltd.), U. S. Patent 2,452,975, Nov. 2, 1948.