Anal. Calcd. for $C_{24}H_{18}O_2$: methoxyl, 8.76. Found: methoxyl, 8.84.

2,4,5-Triphenyl-3-chlorofuran and *n*-Butyllithium.—A solution of 1 g. (0.003 mole) of 2,4,5-triphenyl-3-chlorofuran[9] in 15 cc. of ether was added rapidly to a solution of 0.005 mole of *n*-butyllithium in 15 cc. of ether. The mixture was stirred for one hour and then carbonated in the usual manner to give 0.14 g. (14%) of crude acid melting at 240–245°. After crystallization from glacial acetic acid, the weight of pure acid melting at 257–258° was 0.1 g. (10%). The acid was shown to be identical with that obtained from 2,4,5-triphenyl-3-bromofuran by mixed melting points of the acids and their methyl esters. From the neutral fraction, 0.58 g. (58%) of unchanged 2,4,5-triphenyl-3-chlorofuran was recovered. The high recovery of initial reactant indicates that the yield of halogen–metal interconversion product might be increased appreciably by a longer period of reaction.

3,4,6-Triphenyl-2-bromopyridine and *n*-Butyllithium.—A solution of 3 g. (0.008 mole) of 3,4,6-triphenyl-2-bromopyridine (prepared in accordance with the directions of Kohler and Allen[2]) in 25 cc. of ether was added during five minutes to a solution of 0.017 mole of *n*-butyllithium in 60 cc. of ether, cooled to −35° in a Dry Ice–acetone bath. The solution turned orange-red during the addition and deposited a precipitate about one minute after addition of the halide was complete. Subsequent to stirring for ten minutes at −35°, the mixture was carbonated and worked up in the usual manner. A considerable quantity of white solid (probably the lithium salt of the organic acid), insoluble in dilute potassium hydroxide, was obtained; this was dissolved in hot water and added to the alkaline extract. Acidification of the alkaline extract precipitated 1.82 g. (67%) of acid melting at 166–168° with decomposition. The melting point was not changed after crystallizing a portion from a mixture of benzene and petroleum ether (b. p. 60–68°). The 3,4,6-triphenylpyridine-2-carboxylic acid is readily soluble in ethanol and benzene but only slightly soluble in ether and petroleum ether.

Anal. Calcd. for $C_{24}H_{17}O_2N$: neut. equiv., 351; N, 3.99. Found: neut. equiv., 348 and 349; N, 4.18.

A 0.2-g. portion of the pure acid was heated in an oil-bath at 170–175° until evolution of carbon dioxide ceased and finally for a short time at 185°. The product on crystallization from ethanol gave 0.15 g. (86%) of pure 2,4,5-triphenylpyridine, melting at 111–112°, and identified by a mixed melting point determination with an authentic specimen.[7]

The **methyl 3,4,6-triphenylpyridine-2-carboxylate** was prepared by reaction of a benzene solution of the acid with an ether solution of diazomethane. The ester, which melted at 117–118° after crystallization from dilute methanol, was, like the acid from which it was derived, not appreciably soluble in ether.

Anal. Calcd. for $C_{25}H_{19}O_2N$: N, 3.84. Found: N, 3.98.

Summary

It has been shown that satisfactory yields of RLi compounds are obtainable by the halogen–metal interconversion reaction with 2,4,5-triphenyl-3-bromofuran (which does not react directly with lithium or magnesium) and with 3,4,6-triphenyl-2-bromopyridine (which does not react directly with magnesium).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, INDIANA UNIVERSITY]

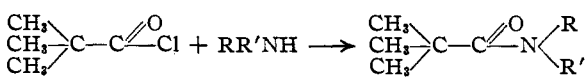
N-Substituted Tri-alkyl Acetamides

BY W. M. DEGNAN[1] AND C. J. SHOEMAKER[2,3]

Fourneau and Florence[4] have shown that the amides of highly branched acids are more effective as sedatives than the amide of the corresponding normal acid. It has also been demonstrated by Whitmore and Homeyer[5] that sedative and hypnotic activity of an amide can be increased if the nitrogen atom is highly substituted. Results of work by Bass[6] showed that *t*-butyl acetamide is inactive; whereas Whitmore and Homeyer[5] have patented certain *t*-butyl acetamides as possible sedative and hypnotic compounds, providing the nitrogen atom carries appropriate groups such as the diethyl or dimethyl groups.

Trimethylacetamide is inactive as a sedative or hypnotic,[7] but as in the case of the *t*-butyl acetamide it was hoped that sedative action would appear if the nitrogen atom were highly substituted. To that end a series of N-substituted trimethylacetamides and N-substituted dimethylethylacetamides were prepared, identified and submitted to pharmacological assay.

The amides were prepared by the familiar Schotten–Baumann reaction. Thus



The hydrogen chloride was removed by several methods. Potassium hydroxide was not completely satisfactory, especially when the amounts involved were small. Better results were obtained by using either potassium carbonate or an excess of the amine. Yields of the amide in most cases were high.

Twelve of the amides were submitted to pharmacological assay by administering them, by mouth, to white rats in amounts varying from 100 to 1500 mg. per kilogram weight of the rat. No sedative action or hypnotic properties were observed in any of the compounds. The N-diethyltrimethylacetamide and trimethylacetyl morpholine caused convulsions.

(1) Dr. Degnan's death occurred on September 30, 1943.

(2) Abstracted from the thesis submitted by Clarence J. Shoemaker to the faculty of the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Doctor of Philosophy.

(3) Now on active duty with the U. S. Navy.

(4) Fourneau and Florence, *Bull. soc. chim.*, **43**, 211 (1928).

(5) Whitmore and Homeyer, U. S. Patent 2,060,154.

(6) Bass, *J. Pharmacol.*, **64**, 50 (1938).

(7) Weil and Rosenthal, *Rocsniki Chem.*, **8**, 44 (1928).

TABLE I

Compound	M. p., °C. (cor.)	Formula	% Nitrogen Calcd.	Found
N-Phenyltrimethylacetamide[a]	132			
N-Phenyldimethylethylacetamide[a]	90			
N-Diethyltrimethylacetamide[b]	[c]			
N-Cyclohexyltrimethylacetamide	122.5	$C_{11}H_{21}NO$	7.65	7.85
N-Cyclohexyldimethylethylacetamide	115	$C_{12}H_{23}NO$	7.11	7.18
N-*p*-Bromophenyltrimethylacetamide[d]	154			
N-*p*-Bromophenyldimethylethylacetamide	102	$C_{12}H_{16}ONBr$	5.19	5.26
N-*o*-Tolyltrimethylacetamide	110	$C_{12}H_{17}NO$	7.34	7.47
N-*o*-Tolyldimethylethylacetamide	119	$C_{13}H_{19}NO$	6.84	6.85
N-2,4-Dimethylphenyltrimethylacetamide	111.5	$C_{13}H_{19}NO$	6.84	7.02
N-2,4-Dimethylphenyldimethylethylacetamide	113.5	$C_{14}N_{21}NO$	6.39	6.24
N-*p*-Tolyltrimethylacetamide[a]	119.5			
N-*p*-Phenetyltrimethylacetamide	105	$C_{13}H_{19}NO_2$	6.33	6.58
N-*p*-Carbethoxyphenyltrimethylacetamide	93	$C_{14}H_{19}NO_3$	5.63	5.78
N-*m*-Nitrophenyltrimethylacetamide	115.5	$C_{11}H_{14}N_2O_3$	12.62	12.83
N-Methyl-N-phenyltrimethylacetamide	82	$C_{12}H_{17}NO$	7.34	7.27
N-Ethyl-N-phenyltrimethylacetamide	67	$C_{13}H_{19}NO$	6.83	6.81
N-Trimethylacetylpiperidine	[e]	$C_{10}H_{19}NO$	8.27	8.56
N-Trimethylacetylmorpholine	73[f]	$C_9H_{17}NO_2$	8.19	8.21
N,N'-Di-trimethylacetyl-*m*-phenylenediamine	186	$C_{16}N_{24}N_2O_2$	10.15	10.13

[a] Underwood and Gale, THIS JOURNAL, **56**, 2117 (1935). [b] Franchimont and Klobbie, *Rec. trav. chim.*, **6**, 243 (1887). [c] B. p. 80–81° (6 mm.), $n^{20}D$ 1.4462. [d] Bryant and Mitchell, THIS JOURNAL, **60**, 2748 (1939). [e] B. p. 115° (10 mm.). [f] B. p. 116° (8 mm.).

Experimental Details

Trimethylacetic Acid.—This material was obtained by the carboxylation of *t*-butylmagnesium chloride as described by Puntambeker and Zoellner.[8]

Trimethylacetyl Chloride.—Trimethylacetic acid was treated with benzoyl chloride as directed by Brown and co-workers.[9] Yields were as high as 60 to 70%.

Dimethylethylacetic Acid.—This acid was prepared by the carboxylation of *t*-amylmagnesium chloride as reported by Bouveault.[10] The yields were lower than in the case of trimethylacetic acid.

Dimethylethylacetyl Chloride.—This chloride prepared by treatment of dimethylethylacetic acid with benzoyl chloride, was distilled off at a temperature of 132° (760 mm.).

N-*p*-Carbethoxyphenyl Trimethylacetamide.—To a vigorously stirred solution of 6.5 g. of ethyl *p*-aminobenzoate in 50 ml. of dry ether 2 g. of trimethylacetyl chloride dissolved in 10 ml. of dry ether was added drop-wise. After refluxing the mixture for two hours, the ether was removed, and the residue treated with a mixture of 25 ml. of water and 5 ml. of concentrated hydrogen chloride. The mixture was allowed to stand overnight and the precipitate was then removed as the impure amide. The amide was recrystallized from 60% ethanol, large white crystals resulted, m. p. 93°, 3.7 g. (89%).

Anal. Calcd. for $C_{14}H_{19}NO_3$: N, 5.63. Found: N, 5.78.

N-Trimethylacetyl Morpholine.—To 9 g. of morpholine dissolved in 60 ml. of dry ether (kept at 5°) was added a solution of 5 g. of trimethylacetyl chloride dissolved in 10 ml. of dry ether. The mixture, after standing for two hours, was treated with 10 ml. of water in order to dissolve the excess amine and morpholine hydrochloride. The ether fraction was removed, dried with calcium chloride, and then fractionally distilled. The N-trimethylacetyl morpholine boiled at 116° at 8 mm. and solidified into a white waxy product, m. p. 73°, 4.5 g. (64%).

Anal. Calcd. for $C_9H_{17}NO_2$: N, 8.19. Found: N, 8.21.

N-*p*-Bromophenyldimethylethylacetamide.—To 5.2 g. of *p*-bromoaniline dissolved in 30 ml. of benzene was added a solution of 2 g. of dimethylethylacetyl chloride dissolved in 15 ml. of benzene. The mixture was stirred and refluxed for two hours. The benzene was removed and the residue was treated with a solution of 5 ml. of concd. hydrochloric acid in 45 ml. of water. The mixture was allowed to stand overnight and the solid was removed by precipitation. The crude amide was recrystallized from 60% ethanol, resulting in very small white crysyals, m. p. 102°, 2.8 g. (75%).

Anal. Calcd. for $C_{12}H_{16}ONBr$: 5.19. Found: N, 5.26.

Acknowledgment.—We wish to acknowledge the assistance of Robert N. Laux for the nitrogen determinations, and the assistance of Mr. E. E. Swanson of the Eli Lilly Company, for the pharmacological assays of the compounds.

Summary

1. Twenty N-substituted trimethylacetamides and N-substituted dimethylethylacetamides were prepared, including fifteen new amides which were identified and characterized.

2. No sedative action was observed in any of the compounds, but N-diethyltrimethylacetamide and N-trimethylacetylmorpholine caused convulsions.

3. Heavy substitution of the nitrogen atom in trimethylacetamide and dimethylethylacetamide does not give rise to sedative or hypnotic compounds.

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(8) Gilman and Blatt, "Organic Syntheses," 2nd. Ed., Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 524.

(9) Brown, THIS JOURNAL, **60**, 1325 (1938).

(10) Bouveault, *Compt. rend.*, **138**, 1108 (1904).