to extract the alcohol adduct, allowed to stand overnight and then was stirred for 24 hours. Water was then added, the ether layer removed, and the aqueous solution was extracted with more ether. The combined ether solutions yielded 1.21 g. of white material (90%), m.p. 164–166°. If the material was worked up immediately after addition was complete, some unreduced starting material was obtained.

An analytical sample of 9,10-dihydro-12-methylol-9,10-ethano-9-methanol (VIII) after recrystallization from benzene melted at 163–163.5° and a mixed melting point with the starting adduct was depressed.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.31; H, 6.86.

The acrylic acid 9-anthraldehyde adduct was reduced with lithium aluminum hydride in a similar fashion as above but was stirred only 3 hours following extraction of the adduct from the soxhlet extractor. From 0.65 g. of adduct, there was obtained 0.56 g. of crude alkali insoluble product, m.p. 154–157°. Recrystallization from benzene led to 0.34 g. of the glycol, m.p. 163–166°. There was no mixed melting point depression with VIII prepared from the allyl alcohol adduct and both gave the same sulfite ester.

Sulfite Ester of VIII.—Two milliliters (0.028 mole) of thionyl chloride was added to 0.20 g. (0.00075 mole) of VIII in 20 ml. of benzene and the solution was heated for 30 minutes. The mixture was evaporated to dryness and 0.20 g. of product, m.p. 209–213°, was obtained. Recrystallization from benzene gave 0.11 g. of white solid, m.p. 223–224°.

Anal. Calcd. for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16; S, 10.26; mol. wt., 312. Found: C, 69.24; H, 5.04; S, 10.14; mol. wt. (Rast), 315 and 338.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

N-Acyl-β-phenethylamines, and a New Isoquinoline Synthesis

BY JOHN J. RITTER AND FRANCIS X. MURPHY[1]

Several N-acyl-α-methyl-β-phenethylamines have been prepared by the reaction of allylbenzene with nitriles in the presence of concentrated sulfuric acid. Three 3,4-dihydroisoquinolines have been obtained by the reaction of methyleugenol with alkoxyaryl nitriles. This is a new synthesis of the isoquinoline ring system. One of these was dehydrogenated to the corresponding known isoquinoline. Amides or dihydroisoquinolines could not be obtained from safrol. A series of sixteen N-acyl-α,α-dimethyl-β-phenethylamines has been prepared from α,α-dimethyl-β-phenethyl alcohol and a group of nitriles.

It has been shown that the reaction of olefins with nitriles to yield N-alkyl amides may be extended to allylbenzene and acetonitrile.[2] Since the product of this reaction is an N-acyl-β-phenethylamine which may be cyclized to 1,3-dimethyl-3,4-dihydroisoquinoline[3] the reaction seemed to offer a new source of intermediates for synthesis of a variety of isoquinolines. Accordingly, the reaction of allylbenzene and substituted allylbenzenes, as safrol and eugenol ethers, with various nitriles was studied with the results reported herein.

TABLE I

N-ACYL-α-METHYL-β-PHENETHYLAMINES, $C_6H_5CH_2CH(CH_3)NHCOR$

R	Proc.	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
C_6H_5	A	54	131–133[a]	$C_{16}H_{17}ON$	80.27	80.02	7.18	7.15	5.85	6.08
$C_6H_5CH_2$	A	53	113–115[b]	$C_{17}H_{19}ON$	80.57	79.91	7.58	7.70	5.53	5.40
3,4-$(CH_3O)_2C_6H_3$	B	53	114–120	$C_{18}H_{21}O_3N$	72.20	72.26	7.08	6.95	4.68	4.82
3,4-$(C_2H_5O)_2C_6H_3$	B	97	149–151	$C_{20}H_{25}O_3N$	73.34	73.41	7.71	7.71	4.28	4.58

[a] Dey and Ramanathan[4] report m.p. 128°, Kalish,[5] 134–135°. [b] Dey and Ramanathan[4] report m.p. 118°.

N-Benzoyl-α-methyl-β-phenethylamine was prepared from allylbenzene and benzonitrile, and N-phenylacetyl-α-methyl-β-phenethylamine from allylbenzene and benzyl cyanide, using concentrated sulfuric acid without a solvent. When the reaction was carried out under the same conditions with allylbenzene and veratronitrile no amide was obtained. The amide resulted in fair yield however when butyl ether was used as solvent in the reaction. The amide from 3,4-diethoxybenzonitrile was prepared in the same manner. Crystalline amides were not obtained from allylbenzene and 4-nitrophenylacetonitrile, diphenylacetonitrile, homoveratronitrile and β-phenylpropionitrile. The two procedures used in reactions carried out with allylbenzene are designated A and B, respectively (Experimental part) and amides so obtained appear in Table I.

One of the amides, N-benzoyl-α-methyl-β-phenethylamine, was cyclized to the dihydroisoquinoline in low yield.

Methyleugenol and benzonitrile seemed to react normally, but several attempts to obtain a crystalline reaction product were unsuccessful. However, when the oily reaction product was distilled *in vacuo* the corresponding dihydroisoquinoline could be isolated from the distillate as its hydrochloride, indicating that the amide had formed in the first step and had been at least partially dehydrated to the

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(1) Abstracted from the thesis presented by Francis X. Murphy in partial fulfillment of the requirements for the degree of Doctor of Philosophy, New York University, February, 1950.

(2) Ritter and Kalish, THIS JOURNAL, **70**, 4048 (1948).

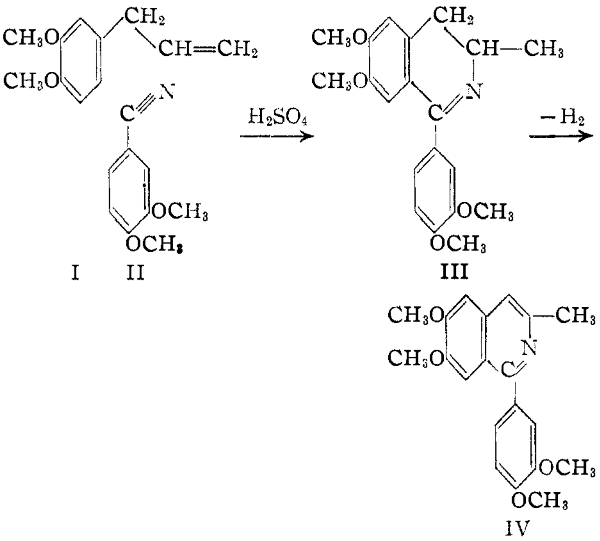
(3) Hey, *J. Chem. Soc.*, 18 (1930).

(4) Dey and Ramanathan, *Proc. Natl. Inst. Sci. India*, **9**, 193 (1943).

(5) Kalish, M.S. Thesis, New York University, 1946.

dihydroisoquinoline on heating. It was found later that distillation is unnecessary, as mere heating under vacuum at high temperature yielded some of the dihydroisoquinoline.

The reaction of methyleugenol (I) and veratronitrile (II) in concentrated sulfuric acid followed by hydrolysis yielded the dihydroisoquinoline (III) directly instead of the expected amide. This appears to be a novel synthesis of an isoquinoline ring system. Dehydrogenation yielded the known compound 1-(3′,4′-dimethoxophenyl)-3-methyl-6,7-dimethoxyisoquinoline (IV), previously obtained by Fodor[6] through a more lengthy procedure.



I II

III

IV

Dihydroisoquinolines were obtained under the same conditions, but in low yields, in the reaction of methyleugenol with anisonitrile and with 3,4-diethoxybenzonitrile. No attempts were made to improve these.

Several attempts to obtain amides or dihydroisoquinolines from safrol were fruitless. As secondary alcohols have been shown[7] to yield N-alkyl amides in reaction with nitriles under the above conditions, an attempt was made, but without successs, to prepare amides from dibenzylcarbinol to serve as intermediates for the preparation of 3-benzylisoquinolines.

Since α,α-dimethyl-β-phenethyl alcohol is known to yield an amide in reaction with hydrogen cyanide and sulfuric acid,[2] its reaction with other nitriles was also investigated. These reactions proceeded readily giving some excellent and many good yields of N-acyl-α,α-dimethyl β-phenethylamines. The majority were carried out in acetic acid solution (procedure C) and certain reactions of alkoxybenzenes in butyl ether (procedure D) with much improved yield. As the N-benzoyl amide in this series was cyclized to the dihydroisoquinoline, the amides shown in Table II should serve as a source of further members of this group. N-Diphenylacetyl-α,α-dimethyl β-phenethylamine (Table II) and the simple N-alkyl diphenylacetamides described in the Experimental Part may be of interest as possible antispasmodics as diphenylacetamide itself has been suggested for that purpose.[8] Schwenk and coworkers[9] have reported the spasmolytic action of a group of N-tertiary alkyl nicotinamides. Two similar compounds have been prepared by us from nicotinonitrile and from 3-cyano-4,6-dimethylpyridone-2 by reaction with α,α-dimethyl-β-phenethyl alcohol (Table II).

TABLE II

N-ACYL-α,α-DIMETHYL-β-PHENETHYLAMINES[a]

$C_6H_5CH_2C(CH_3)_2NHCOR$

R	Yield, %	M.p., °C.	Formula	Anal., N, % Calcd.	Found
$ClCH_2$	87	62.5–64.0	$C_{12}H_{16}ONCl$	6.21	6.30
CH_3	84	91.5–92.0	$C_{12}H_{17}ON$	7.33	7.49
C_2H_3 (vinyl)	90	115.0–115.5	$C_{13}H_{17}ON$	6.89	7.01
H_2NOCCH_2	78	148.5–149.5	$C_{13}H_{18}O_2N_2$	11.96	12.17
C_2H_5	100	97.5–98.5	$C_{13}H_{19}ON$	6.83	6.80
C_3H_7-*n*	94	59.5–60.0	$C_{14}H_{21}ON$	6.39	6.43
C_5H_4N (β-pyridyl)	71	91.0–93.0	$C_{15}H_{18}ON_2$	11.56	11.55[d]
C_6H_5	84	111.5–112.5	$C_{17}H_{19}ON$	5.53	5.72
$4-NO_2C_6H_4CH_2$	93	149.0–150.0	$C_{18}H_{20}O_3N_2$	8.97	8.83
$2-CH_3C_6H_4$	74	70.0–71.0	$C_{18}H_{21}ON$	5.24	5.29
$C_6H_5CH_2$	86	107.0–108.0	$C_{18}H_{21}ON$	5.24	5.35
$4-CH_3OC_6H_4$[b]	81	119.0–121.0	$C_{18}H_{21}O_2N$	4.95	5.20[e]
C_7H_8ON[c]	34	175.0–177.0	$C_{18}H_{22}O_2N_2$	9.39	9.54
$C_6H_5CH_2CH_2$	95	65.0–66.5	$C_{19}H_{23}ON$	4.98	5.22[f]
$3,4-(CH_3O)_2C_6H_3$[b]	71	99.0–101.0	$C_{19}H_{23}O_3N$	4.47	4.62[g]
$(C_6H_5)_2CH$	50	152.0–154.0	$C_{24}H_{25}ON$	4.06	4.18[h]

[a] All prepared by procedure C unless otherwise stated. [b] Procedure D. [c] 2-Hydroxy-4,6-dimethylpyridyl-3. [d] Kjeldahl method with 5-hour digestion. Analyses for carbon and hydrogen on compounds of low nitrogen content are as follows:

	Calcd.: C, %	H, %	Found: C, %	H, %
e	76.27	7.49	76.56	7.52
f	81.08	8.25	81.12	8.21
g	72.80	7.41	72.77	7.47
h	83.67	7.61	83.67	7.47

Experimental Part

N-Benzoyl-α-methyl-β-phenethylamine (Procedure A).—A mixture of 5.9 g. (0.05 mole) of allylbenzene[10] and 5.2 g. (0.05 mole) of benzonitrile was cooled to 10° and 2.7 ml. (0.05 mole) of concentrated sulfuric acid was added gradually with stirring. The cooling bath was then removed and the temperature of the mixture rose spontaneously and was held below 60° by occasional cooling. The resulting deep-red mixture was allowed to stand at room temperature overnight and, after warming briefly on the steam-bath, it was poured into water, neutralized with sodium carbonate and the crystalline product was filtered, washed with ice-water several times and dried *in vacuo*. It weighed 6.5 g. (54% of calcd.). A portion recrystallized from benzene and then from 50% ethanol melted at 131–133°. Dey and Ramanathan[4] reported m.p. 128°, and Kalish[5] reported m.p. 134–135° for this compound.

N-(3′,4′-Diethoxybenzoyl)-α-methyl-β-phenethylamine (Procedure B).—Finely ground 3,4-diethoxybenzonitrile[11] (7.6 g., 0.04 mole) was suspended in 5.4 ml. (0.04 mole) of allylbenzene and the rapidly stirred mixture was cooled to 5°. A cooled solution of concentrated sulfuric acid (5.0 ml.) in an equal volume of butyl ether was then added at once. As there was no appreciable spontaneous temperature rise, the deep red mixture was heated externally to 75° during 30 minutes and held at this temperature for about ten minutes. After standing overnight the semi-solid mixture was softened by warming, poured into water and neutralized with sodium carbonate. The crystalline amide (12.7 g., 97% of calcd.) which precipitated was filtered,

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[6] Fodor, *Acta. Lit. Sci. Regiae Univ. Hung. Francisco-Josephine, Sect. Chem. Mineral. Phys.*, **6**, 1 (1937); *C. A.*, **32**, 2124 (1938).

[7] Benson and Ritter, THIS JOURNAL, **71**, 4128 (1949); Hartzell and Ritter, *ibid.*, **71**, 4130 (1949).

[8] Lespagnol and Ponthieu, *Bull. soc. chim.*, **11**, 541 (1944).

[9] Schwenk, *et al.*, Abstracts of the Am. Chem. Soc. Meeting at Atlantic City, N. J., Sept., 1949, p. 31.

[10] Hershberg, *Helv. Chim. Acta*, **17**, 352 (1934).

[11] Prepared from 3,4-diethoxybenzaldehyde (Eastman Kodak Co.) by the method of Buck and Ide, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 108.

washed several times with cold water and dried *in vacuo*. After three recrystallizations from aqueous methanol it melted at 149–151°.

1-Phenyl-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline.—To 6.2 ml. (0.06 mole) of benzonitrile cooled in an ice-bath concentrated sulfuric acid (3.3 ml., 0.06 mole) was added slowly. The ice-bath was removed and the mixture was stirred rapidly at 20° while methyleugenol (10.1 ml., 0.06 mole) was added over 3–4 minutes. The temperature rose spontaneously during the addition and was held around 60° by intermittent cooling. After two days at room temperature, a viscous oil which separated was extracted with warm benzene, the benzene layer was separated and filtered and the benzene removed. The residue was distilled at 18 mm. yielding a heavy oil at 150°. The distillate was dissolved in 25 ml. of acetone and treated with dry hydrogen chloride. The dihydroisoquinoline hydrochloride (2.8 g., 14.5% of calcd., m.p. 259–263°) separated as pale yellow crystals which were filtered, washed with acetone and dried *in vacuo*.

1-(3′,4′-Dimethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (III).—Veratronitrile (9.8 g., 0.06 mole) was added portionwise to concentrated sulfuric acid (15 ml.) in an ice-bath with rapid stirring. Methyleugenol (10.2 ml., 0.06 mole) was then added during two minutes. The cooling bath was removed before addition of the methyleugenol and the temperature, which rose rapidly during the addition, was maintained around 80° by intermittent cooling. After standing at room temperature for three days the reaction mixture was poured into water and neutralized with sodium carbonate. A yellow mass separated which gradually crystallized on stirring in warm water. It was filtered, washed with water and dried. The crude dihydroisoquinoline (11.5 g., 53% of calcd.) was crystallized from aqueous ethanol as yellow crystals (6.7 g.) melting at 134–137°. Recrystallization yielded a product melting at 138–139°.

Anal. Calcd. for $C_{20}H_{23}O_4N$: C, 70.33; H, 6.81; N, 4.11. Found: C, 70.49; H, 6.99; N, 3.97.

The hydrochloride was obtained by evaporating a solution of the base in dilute hydrochloric acid to small volume. Recrystallization from water containing a small amount of hydrochloric acid gave small canary-yellow needles, m.p. 185–186° (dec.).

Anal. Calcd. for $C_{20}H_{24}O_4NCl$: N, 3.71. Found: N, 3.91.

1-(4′-Methoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline.—This compound was prepared by the procedure used for (III). A gummy reaction product was obtained which crystallized partly from warm water and the suspension of crystals (2.0 g.) was decanted from the remaining gum. A further crop (0.9 g.) was obtained by dissolving the gum in ethanol and adding water. After two recrystallizations from aqueous ethanol the compound melted at 104–105°.

1-(3′,4′-Diethoxyphenyl)-3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline.—The product from 3,4-diethoxybenzonitrile and methyleugenol using the procedure described above was a gummy solid. Only 3,4-diethoxybenzamide (m.p. 187–188°) was recovered from this. The aqueous filtrate from which the primary product had been removed slowly deposited pale yellow needles (0.24 g.) which proved to be the dihydroisoquinoline. Recrystallization from aqueous ethanol gave fine white needles, m.p. 104°.

1-(3′,4′-Dimethoxyphenyl)-3-methyl-6,7-dimethoxyisoquinoline (IV).—The dihydroisoquinoline base (III) (0.20 g.) and 0.2 g. of 5% palladium-on-activated-charcoal catalyst were placed in a flask with 10 ml. of tetralin. The mixture was refluxed one hour and the cooled solution was filtered. After washing the catalyst with warm toluene the combined filtrate and wash was treated with 5 ml. of dilute hydrochloric acid. In a few days the lower (aqueous) layer deposited rosettes of yellow needles. The oil layer was decanted and the crystals were filtered, washed sparingly with ice-water and dried *in vacuo*. The product weighed 0.15 g. and melted at 197–198° (dec.). Fodor[6] reported the melting point as 193°.

Anal. Calcd. for $C_{20}H_{21}O_4N \cdot HCl \cdot 2H_2O$: C, 58.29; H, 6.38; N, 3.40. Found: C, 58.07, 57.91; H, 6.67, 6.40; N, 3.33.

N-Benzoyl-α,α-dimethyl-β-phenethylamine (**Procedure C**).—To a mixture of α,α-dimethyl-β-phenethyl alcohol[12] (4.5 g., 0.03 mole) and benzonitrile (3.1 g., 0.03 mole) in 5 ml. of glacial acetic acid, 2.0 ml. of concentrated sulfuric acid was added with stirring. The temperature of the mixture rose to 70° over several minutes. Around 50° the mixture became turbid and when stirring was interrupted a clear colorless upper layer formed. As stirring continued a single clear phase formed at 65°. After standing for four hours the mixture was poured on ice and neutralized with sodium carbonate, yielding a crystalline mass which was filtered, washed with water and dried *in vacuo*. It weighed 6.4 g. (84% of calcd.) and melted at 112–113°, both before and after recrystallization from benzene.

N-(3′,4′-Dimethoxybenzoyl)-α,α-dimethyl-β-phenethylamine (Procedure D).—A mixture of α,α-dimethyl-β-phenethyl alcohol (4.5 g., 0.03 mole), veratronitrile (4.9 g., 0.03 mole) and 5.0 ml. of butyl ether was warmed to dissolve the reactants and cooled to room temperature. Gradual addition of 2.0 ml. of concentrated sulfuric acid to the stirred solution caused a temperature rise of 60° where a separation into two layers occurred. After standing overnight at room temperature the upper (butyl ether) layer was decanted and discarded. The brown semi-solid lower layer was poured on ice and neutralized with sodium carbonate. The mixture was warmed for a short time and separated an oil which slowly crystallized in the refrigerator. The crystals (6.7 g., 71% of calcd.) were filtered and after washing with water and drying melted at 97–100°. A portion recrystallized from benzene–petroleum ether mixture melted at 99–101°.

N-*t*-Butyldiphenylacetamide.—A mixture of 2.2 g. (0.03 mole) of *t*-butanol and 5.8 g. (0.03 mole) of diphenylacetonitrile[13] in 6.5 ml. of glacial acetic acid was stirred and treated with 2.0 ml. of concentrated sulfuric acid. After standing at room temperature overnight it was poured on ice and neutralized with sodium bicarbonate. The resulting crystalline product (8.0 g., 100% of calcd.) was filtered and after washing with water and drying melted at 197–199°. A portion recrystallized from benzene melted at 201–202°.

Anal. Calcd. for $C_{18}H_{21}ON$: N, 5.24. Found: N, 5.39.

N-*t*-Amyldiphenylacetamide.—This compound was prepared by the method given in the preceding paragraph; yield 76%; m.p. 180°.

Anal. Calcd. for $C_{19}H_{23}ON$: N, 4.98. Found: N, 5.30.

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[12] Klages, *Ber.*, **37**, 1723 (1904).

[13] M.p. 78–79°; reported m.p. 75–76°.