while cooling with a water bath. After stirring for 10 min., the red-orange solid which had formed was quickly filtered, washed with dry ether, and at once returned to the reaction flask and suspended in a fresh 200-ml. portion of dry ether. To this mixture was added slowly and with stirring a solution of 12.5 ml. of anhydrous dimethylamine in 25 ml. of dry ether. After stirring for 0.5 hr., the solid product was collected by filtration, washed with ether, slurried with water, refiltered, washed with water and ether, and then recrystallized from tetrahydrofuran-ether; yield, 20 g. (75%) of white, cotton-like needles; m.p. 223–223.5°.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.7; H, 6.0; N, 11.2.

5-Methoxy-N,N-dimethyltryptamine (XII). To a stirred mixture of 11.7 g. of lithium aluminum hydride and 250 ml. of dry ether was added portionwise and cautiously a suspension of 18.5 g. of XI in 200 ml. of hot dry benzene, using additional dry ether to transfer the last of the solid. The reaction mixture was stirred and refluxed for 1.5 hr. longer, cooled in an ice bath, and cautiously treated with water to hydrolyze excess $LiAlH_4$ and the reaction complex. The ether-benzene solution of the product was filtered from the insoluble inorganic matter, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to a residue of crude XII, which solidified on cooling; yield, 15 g. (91%). A portion of the crude product was converted to its hydrochloride salt, which was recrystallized from alcohol-ether; m.p. 145–146°.

Anal. Calcd. for $C_{13}H_{19}ClN_2O$: Cl, 13.9. Found: Cl, 14.0.

1-Methyl-5-methoxy-N,N-dimethyltryptamine (XIII). *From* XII. A suspension of $NaNH_2$ in liquid ammonia was prepared from 1 g. of clean sodium, 150 ml. of liquid ammonia, and 0.1 g. of ferric nitrate. To this mixture was added portionwise 6 g. of crude XII dissolved in 20 ml. of dry ether. After stirring for 5 min., 3 ml. of methyl iodide was added slowly, and the ammonia was allowed to evaporate. The residue was treated with water, and the product extracted from this mixture with ethyl acetate and chloroform. After drying over anhydrous $MgSO_4$ and filtration, treatment with dry HCl precipitated crude XIII as its HCl salt. Recrystallization from alcohol-ether afforded 3.7 g. of 1-methyl-5-methoxy-*N,N*-dimethyltryptamine hydrochloride (50%), m.p. 196–196.5°, unchanged after one more recrystallization from alcohol-ether.

Anal. Calcd. for $C_{14}H_{21}ClN_2O$: Cl, 13.2; N, 10.4. Found: Cl, 13.1; N, 10.0.

From bufotenine (VII). To a suspension of $NaNH_2$ in 150 ml. of liquid ammonia prepared from 1.6 g. of clean sodium was added 6.1 g. of bufotenine, which had been obtained by hydrogenolysis of *O*-benzylbufotenine hydrochloride with hydrogen and 10% Pd-C.[6] After stirring for several minutes, 5 ml. of methyl iodide was added slowly, and the ammonia allowed to evaporate. The dark brown residue was treated with water and ether, the ether extract was separated and dried, and treated with anhydrous HBr. A very dark oil separated; attempts to purify it were futile. Finally, a sample was converted to the free base and a picrate obtained, which melted at 206–207° (dec.) after several recrystallizations from acetone-water; this picrate was identical to a specimen prepared from the product obtained from XII, m.p. 206–207° (dec.), no depression on mixed melting point.

Anal. Calcd. for $C_{26}H_{23}N_5O_8$: C, 52.0; H, 4.99; N, 15.19. Found: C, 52.0; H, 4.99; N, 15.17.

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COLUMBUS 1, OHIO

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE FELS RESEARCH INSTITUTE]

Psychopharmacological Activity of Ring- and Side Chain-Substituted β-Phenethylamines[1]

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Synthesis of a number of ring-substituted β-phenethylamines containing alkyl, halogen, and alkoxy substituents by various methods is described. The influence of these ring substituents on the psychotomimetic activity of substituted β-phenethylamines was examined by observing the effect of these compounds on cat behavior.

To obtain additional information on the influence of both the nature and position of substituents on ring- and side chain-substituted β-phenethylamines on the psychotomimetic activity of this class of compounds, a series of β-phenethylamines containing a variety of substituents in the 3, 4, and 5 positions was synthesized. Substituents which were examined included alkyl, phenyl, halogen, and alkoxy in varying positions on the benzene ring in β-phenethylamine; a few compounds were also made with hydroxy or methyl groups in the side chain which are related to epinephrine and amphetamine. The effect of these compounds on normal cat behavior[4] was used as an index to the changes in psychochemical activity induced by the various substituents.

Synthesis. Most of the *p*-alkyl and halogen-substituted β-phenethylamines studied were obtained by chloromethylation of the appropriately substituted benzene, conversion of the resulting sub-

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(4) S. Norton and E. J. deBeer, *Ann. N. Y. Acad. Sci.*, 65, 249 (1956).

TABLE I
RING-SUBSTITUTED β-PHENETHYLAMINES

Substituents	Method	M.P. HCl Salt	Analyses							
			Calculated				Found			
			C	H	N	Cl	C	H	N	Cl
2-Methyl	II	226°[a]								
3-Methyl	II	170–171°[b]								
4-Methyl	I	217–218°[c]								
4-Ethyl	I	208–209°[d]								
4-Isopropyl	I	266–268°[e]								
4-*tert*-Butyl	I	258–260° (dec.)			6.6	16.6			6.7	16.7
4-*n*-Hexyl	I	175–177°			5.8	14.7			5.9	14.9
4-Phenyl	I	293–295°			6.0	15.2			6.0	15.1
4-Fluoro	I	212–213°[f]								
4-Chloro	I	218–218.5°[g]								
4-Bromo	I	240–243° (dec.)	40.6	4.7	5.9	15.0	40.6	4.6	5.6	15.1
4-Iodo	I	294–296° (dec.)	33.9	3.9	4.9	12.5	34.2	3.7	4.7	12.8
3,5-Dibromo-4-hydroxy	[h]	269–270° (dec.)[i]								
3,5-Dibromo-4-methoxy	[j]	233–234°	31.3	3.5	4.0		31.4	3.4	3.9	
3,5-Dimethyl-4-methoxy	[j]	226–227°			6.5	16.5			6.4	16.4
3,5-Dimethoxy	II	156–157°			6.5	16.4			6.3	16.7
3,4-Methylenedioxy	III	213–214°[k]								
3,4,5-Triethoxy	[j]	172–173°[l]								
DL-3,4,5-Trimethoxy-β-methyl	III	220–221°[m]								
DL-3,4,5-Trimethyl-β-methyl	III	265–266°			6.5	16.6			6.3	16.6
DL-3,4-Methylenedioxy-β-methyl	III	191–192°[n]								
3,4-Dimethyl-α-hydroxy-*N*-methyl	[j]	121–122°			6.5	16.5			6.5	16.5
3,4,5-Trimethyl-α-hydroxy-*N*-methyl	[j]	186–187°			6.1	15.5			5.9	15.3
3,4-Dimethyl-α-hydroxy	[j]									

[a] Reported[6] m.p. 227°; [b] reported[7] m.p. 160°; [c] reported[8] m.p. 217–218°; [d] reported[8] m.p. 208°; [e] reported[9] m.p. 270°; [f] reported[10] m.p. 206–208°; [g] reported[11] m.p. 215° (dec.); [h] reported[5] m.p. 270°; [i] HBr salt; [j] see experimental section; [k] reported[12] m.p. 210–211°; [l] reported[13] m.p. 175°; [m] reported[14] m.p. 219–220°; [n] reported[15] m.p. 180–181°.

stituted benzyl chloride to the corresponding phenylacetonitrile, and finally, reduction of the latter to the corresponding β-phenethylamine with lithium aluminum hydride (Method I). In several cases the starting compound was a substituted benzoic acid, which was converted to the corresponding phenylacetamide *via* the Arndt-Eistert synthesis; reduction of the amide with lithium aluminum hydride furnished the desired β-phenethylamine (Method II). A third route started with a substituted benzaldehyde, which was condensed with either nitromethane or nitroethane, and the resulting nitroolefin reduced to the amine with lithium aluminum hydride (Method III).

3,5-Dibromo-4-hydroxy-β-phenethylamine was obtained by bromination of tyramine;[5] preferential *N*-acetylation of this compound, followed by methylation of the phenolic hydroxyl with methyl sulfate and alkali, and finally deacetylation with dilute hydrochloric acid afforded 3,5-dibromo-4-methoxy-β-phenethylamine. 3,5-Dimethyl-4-methoxy-β-phenethylamine was obtained from 2,6-dimethylphenol in the following sequence of reactions: *O*-acetylation, Fries rearrangement of the resulting phenyl acetate, *O*-methylation, a Kindler-modified Willgerodt reaction, hydrolysis of the thiomorpholide to the phenylacetic acid, conversion to amide, and finally reduction to the amine with lithium aluminum hydride. 3,4-Dimethyl- and 3,4,5-trimethyl-α-hydroxy-N-methyl β-phenethylamines were obtained from the corresponding substituted acetophenones *via* bromination to the corresponding phenacyl bromides which were treated with *N*-methylbenzylamine to give the amino ketones, and finally simultaneous debenzylation and reduction of the carbonyl group to secondary alcohol by catalytic hydrogenation over a palladium-carbon catalyst. Table I lists the various substituted β-phenethylamines synthesized.

Pharmacological results. The pressor activity of

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(6) H. Emde, *Ann.*, **391**, 105 (1912).
(7) A. F. Titley, *J. Chem. Soc.*, 516 (1926).
(8) J. H. Speer and A. J. Hill, *J. Org. Chem.*, **2**, 139 (1937).
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(11) J. S. Buck, *J. Am. Chem. Soc.*, **55**, 2593 (1933).
(12) K. Kindler, *Arch. der Pharm.*, **1927**, 397.
(13) K. H. Slotta and G. Szyzka, *J. Prakt. Chem.*, **137**, 399 (1933).
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this series of amines was determined on a nembutalized cat preparation by means of the manometrically observed variations in blood pressure taken at the carotid artery. All of the amines were administered intravenously at a dose level of 0.1–0.5 mg. as the hydrochloride salt and comparisons were made in the same preparation against β-phenethylamine hydrochloride (0.1 mg.) as a standard. For the most part all of the amines within this series exhibited less than 60 per cent of the pressor activity of the standard; 3-methyl-β-phenethylamine, the most active compound in this respect, showed 90 per cent of the pressor action of β-phenethylamine. Both *N*-methyl-3,4-dimethyl- and 3,4,5-trimethyl-β-phenylethanolamine gave a prompt increase in the observed blood pressure which gradually returned to normal. In contrast, 4-*n*-hexyl- and 4-phenyl-β-phenethylamine produced a very slight pressor action in which the preparation showed a slow increase and decrease in blood pressure. The pressure activity was not increased by pretreatment of the test animals with iproniazid (40 mg./kg.) thus indicating that pressor action within this series is not directly dependent upon the level of β-amine oxidase.

In the course of making the pressor action measurements, it was noted that nearly all these β-phenethylamine derivatives exhibited an analeptic activity in the nembutalized cat at a low level of anesthesia. This was concluded from the fact that repeated injections of nembutal were required to maintain both the blood pressure and reflexes at a reasonable level.

Table II summarizes the behavioral changes which were observed in normal, healthy, adult cats of both sexes which were used as a measure of compound activity. The behavioral components of pilomotor activity, salivation, pupil dilation, growling, hissing, withdrawal, and aggressive behavior were chosen as measures of the over-all behavioral pattern of the animal. Norton and deBeer[4] have discussed the use of these parameters in drug evaluation. Compounds which produced a positive response in all of these components at a dose level of 25 mg./kg. by intramuscular injection were considered to be rage producing drugs. At this dose level, none of the compounds caused acute toxic reactions. Among the compounds examined within this series, the following gave strong rage response: 3-methyl-, 4-methyl-, 4-chloro-, and 3,5-dimethyl-4-methoxy-β-phenethylamine. The latter compound shows very weak pressor activity. 4-*n*-Hexyl-β-phenethylamine produced the behavioral pattern characteristic of rage without pupil dilation or salivation, and the effect was maintained for a longer time. Compounds which produced virtually no apparent change in the normal behavioral pattern included 4-*t*-butyl-, 4-phenyl-, 4-fluoro-, 4-iodo-, 3,5-dibromo-4-hydroxy-, 3,4,5-triethoxy-, 3,5-dimethoxy-, *N*-methyl-3,4-dimethyl-α-hydroxy-, and *N*-methyl-3,4,5-trimethyl-α-hydroxy-β-phenethylamine. Ethyl-, isopropyl, and *t*-butyl groups in the 4-position of β-phenethylamine produced progressively less rage response in cats. Although 4-bromo- and 3,5-dibromo-4-methoxy-β-phenethylamine were not devoid of activity, they did not produce typical rage reactions. The latter compound shows a depressant effect rather than pressor activity.

A rather unique change in behavior was produced by 3,4,5-trimethylamphetamine; animals receiving this compound demonstrated all of the characteristic rage responses without aggressive behavior. This pattern suggests the production of only the fear components of the rage reaction.

The introduction of methyl groups into the 3- or 4-positions of β-phenethylamine induces dramatic behavioral changes which are best classified as a rage response. This observation has prompted an investigation of the activity of ring polymethylated β-phenethylamines, particularly in connection with their possible psychotomimetic activity.

EXPERIMENTAL[16]

4-Ethyl-β-phenethylamine (*Method* I). The procedure described for synthesis of this compound is representative of that used to obtain all compounds prepared by Method I. Ethylbenzene was chloromethylated with paraformaldehyde and HCl in the presence of fused and powdered $ZnCl_2$ by the procedure of Blanc[17] to obtain 4-ethylbenzyl chloride, b.p. 99–102°/17 mm., in 72% yield. Treatment with sodium cyanide in an aqueous alcohol medium by a standard procedure[18] resulted in an 80% yield of 4-ethylphenylacetonitrile, b.p. 134–136°/15 mm. To a stirred suspension of 19 g. of powdered lithium aluminum hydride in 600 ml. of absolute ether was added slowly 36 g. of 4-ethylphenylacetonitrile. After refluxing for 0.5 hr., the reaction mixture was cooled in an ice bath and hydrolyzed by slow and careful addition of water. The precipitated lithium metaluminate was removed by filtration, washing the cake well with ether. The ether solution was then dried over anhydrous $MgSO_4$, filtered, and treated with dry HCl gas to obtain the product in the form of the hydrochloride salt; yield, 23.3 g. (50%). For final purification the hydrochloride salt was recrystallized from ethanol or ethanol-ethyl acetate; m.p. 208–209°.[8]

Yields were similar for other compounds synthesized by this method. 4-Bromo- and 4-iodobenzyl bromides were obtained by bromination of *p*-bromo- and *p*-iodotoluene respectively.[19] All of the required substituted benzyl chlorides were prepared by the chloromethylation reaction.

3-Methyl-β-phenethylamine (*Method* II). A mixture of 25 g. of *m*-toluic acid and 30 ml. of thionyl chloride was refluxed for 3 hr.; after removal of excess thionyl chloride by distillation, the residue was distilled under reduced pressure to give 26.7 g. (93%) of *m*-toluyl chloride, b.p. 115–116°/30 mm. An absolute ether solution of the acid chloride was added to a cold ether solution containing 17.6 g. (0.42 mole) of diazomethane. After standing overnight at room temperature, ether was removed under reduced pressure and

(16) Melting points are uncorrected. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill.

(17) G. Blanc, *Bull. soc. chim.*, (4) **33**, 313 (1923).

(18) R. C. Fuson and N. Rabjohn, *Org. Syntheses*, **Coll. Vol. III**, 558 (1955).

(19) M. Weizmann and S. Patai, *J. Am. Chem. Soc.*, **68**, 150 (1946); H. A. Sloviter, *J. Am. Chem. Soc.*, **71**, 3360 (1949).

TABLE II

Compounds[a]	Pilo-Motor	Pupil Dilatation	Growl	Hiss	Aggressive Behavior	Withdrawing	Salivation
Phenethylamines							
3-Methyl	++	++	++	++	++	++	++
2-Methyl	++	++	0	0	0	++	0
4-Methyl	++	++	++	++	++	+	++
4-Ethyl	+	++	0	0	0	+	0
4-Isopropyl	++	++	+	0	0	+	+
4-*tert*-Butyl	++	0	0	0	0	+	+
4-Hexyl	+	0	+	++	++	++	0
4-Phenyl	0	0	0	0	0	0	0
4-Fluoro	+	0	0	0	0	+	++
4-Chloro	++	++	++	++	++	++	++
4-Bromo	+	++	+	0	0	+	++
4-Iodo	0	0	0	0	0	+	0
3,5-Dibromo-4-hydroxy	0	0	0	0	0	0	0
3,5-Dibromo-4-methoxy	+	++	+	0	0	++	0
3,5-Dimethyl-4-methoxy	++	++	++	++	++	++	++
3,4,5-Triethoxy	0	0	0	0	0	0	0
3,5-Dimethoxy	0	0	0	0	0	+	0
3,4-Methylenedioxy	++	++	0	++	0	++	+
Phenethanolamines							
3,4-Dimethyl(*N*-methyl)	++	0	0	0	0	0	+
3,4,5-Trimethyl(*N*-methyl)	+	0	0	0	0	0	0
Phenylisopropylamines							
3,4,5-Trimethyl	++	++	+	++	0	++	++
3,4,5-Trimethoxy	0	+	0	++	0	++	+
3,4-Methylenedioxy	++	++	0	0	0	++	+

[a] All compounds given 25 mg. per kg. intramuscular.

the residual yellow solid diazoketone was crystallized from benzene-petroleum ether (30–60°); yield, 19.6 g. (71%); m.p. 69–70°. The diazoketone was refluxed overnight in a mixture of 50 ml. of purified dioxane, 280 ml. of 28% aqueous ammonia, and 28 ml. of 10% $AgNO_3$. The hot solution was treated with Norite, filtered, concentrated to about one half its volume, and allowed to cool to crystallize the product; yield of 3-methylphenylacetamide, m.p. 147–148° (reported[20] 141°), 14.6 g. (80%). A solution of the amide in 325 ml. of boiling dry reagent benzene was added portionwise to a stirred suspension of 11.6 g. of lithium aluminum hydride in 250 ml. of absolute ether. The reaction mixture was refluxed for 0.5 hr., cooled in an ice bath, hydrolyzed by cautious addition of water, and filtered from inorganic material. After drying over anhydrous $MgSO_4$, the ether solution was treated with dry HCl gas to precipitate the product as the solid hydrochloride salt; yield, 13.7 g. (85%); m.p. 170–171°, after recrystallization from ethanol-ethyl acetate.

2-Methyl- and 3,5-dimethoxy-β-phenethylamine were obtained similarly from the corresponding benzoic acids.

3,4-Methylenedioxy-β-phenethylamine (*Method* III). This method has been described by Ramirez and Burger[21] for obtaining β-phenethylamines by reduction of β-nitrostyrenes with lithium aluminum hydride. 3,4-Methylenedioxy-β-nitrostyrene, m.p. 160–161°, was obtained in 86% yield from piperonal and nitromethane in the presence of alkali by the procedure described for preparation of β-nitrostyrene.[22] To a stirred suspension of 23 g. of lithium aluminum hydride in 400 ml. of absolute ether was added portionwise a solution of 32 g. of 3,4-methylenedioxy-β-nitrostyrene in about 400 ml. of boiling benzene. The mixture was refluxed for 1 hr., cooled in an ice bath, hydrolyzed cautiously with water, filtered, dried over anhydrous $MgSO_4$, and treated with dry HCl gas to obtain the product as the hydrochloride salt; yield, 20.5 g. (62%); m.p. 213–214°, after recrystallization from ethanol-ethyl acetate. Other compounds prepared by Method III were obtained by similar procedures.

3,5-Dibromo-4-hydroxy-β-phenethylamine.[5] A solution of 13.7 g. of tyramine in 85 ml. of acetic acid was treated portionwise with a solution of 32 g. of bromine in 90 ml. of acetic acid until color of excess bromine persisted. When the mixture was cooled, solid 3,5-dibromo-4-hydroxy-β-phenethylamine hydrobromide was deposited, and it was collected and washed with ether; yield, 31.2 g. (83%); m.p. 269–270° (dec.).

3,5-Dibromo-4-methoxy-β-phenethylamine. To a solution of 28.2 g. of 3,5-dibromo-4-hydroxy-β-phenethylamine hydrobromide in 600 ml. of water at 70° was added 20 ml. of acetic anhydride and then a solution of 18 g. of sodium acetate in 50 ml. of water. An oil separated which was extracted with ether, the ether solution washed with water, and the solvent evaporated to leave a residue which slowly crystallized; yield, 16.5 g. (65%); m.p. 147–148°. To a solution of 15.2 g. of *N*-acetyl-3,5-dibromo-4-hydroxy-β-phenethylamine in 3 g. of NaOH and 80 ml. of water was added 10 ml. of methyl sulfate in 3 portions. After standing several hours, crystalline *N-acetyl-3,5-dibromo-4-methoxy-β-phenethylamine* was deposited; yield, 13.7 g. (87%); m.p. 121–122°, after recrystallization from alcohol.

Anal. Calcd. for $C_{11}H_{13}Br_2NO_2$: C, 37.6; H, 3.7; N, 4.0. Found: C, 37.4; H, 3.6; N, 4.1.

A mixture of 12 g. of crude *N*-acetyl-3,5-dibromo-4-methoxy-β-phenethylamine and 70 ml. of 1:1 hydrochloric acid was refluxed for 1 hr. Upon cooling, a crystalline product precipitated and was collected, washed, and dried; yield of 3,5-dibromo-4-methoxy-β-phenethylamine hydrochloride, 8.9 g. (75%); m.p. 233–234°, after recrystallization from ethanol–ethyl acetate.

3,5-Dimethyl-4-methoxy-β-phenethylamine. A mixture of 100 g. of 2,6-dimethylphenol and 150 ml. of acetic anhydride

(20) Br. Radziazswski and P. Wispek, *Ber.*, **18**, 1279 (1885).

(21) F. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2782 (1950).

(22) D. E. Worral, *Org. Syntheses*, **Coll. Vol. I** (2nd ed.), 413 (1943).

was refluxed for 3.5 hr. and then distilled under reduced pressure. The fraction boiling at 83–85°/0.6 mm. was collected as 2,6-dimethylphenyl acetate; yield, 108 g. (80%). A mixture of this product and 93 g. of anhydrous $AlCl_3$ was warmed on a steam bath to initiate reaction and allowed to react at room temperature for 2 hr. After heating on a steam bath for an additional 0.5 hr., the mixture was poured onto ice and HCl. The crude solid product was collected and recrystallized from methanol-water to obtain pale yellow plates of 3,5-dimethyl-4-hydroxyacetophenone; yield, 76.5 g. (71%); m.p. 154–154.5°; reported[23] m.p. 150–151°. To a cold solution of 75 g. of this product in 100 ml. of methanol and 100 ml. of methyl sulfate was added a solution of 80 g. of NaOH in 90 ml. of water at a temperature below 30°. The mixture was then refluxed for 15 min. and diluted to a volume of about 1200 ml. with water. The oil which separated was extracted with ether, and the residue remaining after evaporation of the ether crystallized; yield of *3,5-dimethyl-4-methoxyacetophenone*, 66 g. (80%); m.p. 47–48°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.1; H, 7.9.

A mixture of 65.4 g. of this ketone, 47 g. of redistilled morpholine, and 17 g. of sulfur was refluxed for 7 hr., and then poured into 200 ml. of hot ethanol. The crude solid product which separated was collected and recrystallized from ether–petroleum ether; yield of *3,5-dimethyl-4-methoxy phenylthioacetomorpholide*, 65 g. (65%); m.p. 86–87°.

Anal. Calcd. for $C_{15}H_{21}NO_2S$: N, 5.0; S, 11.5. Found: N, 5.1; S, 11.3.

A mixture of 56.7 g. of the thiomorpholide, 110 ml. of glacial acetic acid, 25 ml. of water, and 15 ml. of concentrated H_2SO_4 was refluxed for 7.5 hr., cooled, and poured into 800 ml. of water. The dark oil which separated was extracted with ether, and this solution was extracted with dilute aqueous NaOH. Acidification with HCl precipitated *3,5-dimethyl-4-methoxyphenylacetic acid;* yield, 34.5 g. (89%); m.p. 77–78°, after vacuum distillation and recrystallization from ether–petroleum ether (30–60°).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.1; H, 7.2. Found: C, 67.9; H, 7.3.

A mixture of 18 g. of the acid, 14 ml. of thionyl chloride, and 60 ml. of chloroform was refluxed for 3 hr., stripped of solvent and excess thionyl chloride, and added slowly to a large excess of aqueous ammonia at a temperature not exceeding 20°. The solid product was collected, washed, and air dried; yield of *3,5-dimethyl-4-methoxyphenylacetamide*, 14 g. (81%); m.p. 109–110°, after recrystallization from benzene–petroleum ether (30–60°).

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.25.

A solution of 14 g. of the amide in 200 ml. of dry reagent benzene was added gradually to a stirred suspension of 8.3 g. of lithium aluminum hydride in 300 ml. of absolute ether. After refluxing for 1 hr., the mixture was cooled, hydrolyzed cautiously with water, and inorgnic salts removed by filtration. The filtrate was dried over anhydrous $MgSO_4$, and the product was obtained as the hydrochloride salt by addition of dry HCl gas; yield, 15.7 g. (76%); m.p. 226–227°, after recrystallization from ethanol–ethyl acetate.

3,4,5-Triethoxy-β-phenethylamine. A mixture of 16 g. of 3,4,5-triethoxyphenylacetic acid,[24] 10 ml. of thionyl chloride, and 20 ml. of chloroform was refluxed for 1 hr., the excess thionyl chloride and chloroform were distilled off under reduced pressure, and the residue was added to 50 ml. of aqueous ammonia. The crude solid product was collected and recrystallized from benzene–petroleum ether; the yield of *3,4,5-triethoxyphenylacetamide* was 10.2 g. (64%); m.p. 137–138°.

Anal. Calcd. for $C_{14}H_{21}NO_4$: C, 62.9; H, 7.9; N, 5.2. Found: C, 62.8; H, 7.8; N, 5.2.

A solution of 8 g. of the amide in 100 ml. of boiling dry reagent benzene was added to a stirred suspension of 3.8 g. of lithium alnminum hydride in 150 ml. of absolute ether. The mixture was stirred for an additional 2 hr., cooled in an ice bath, and hydrolyzed by cautious addition of water. The inorganic salts were removed by filtration, the filtrate was dried over anhydrous $MgSO_4$, and the product precipitated as the hydrochloride salt by treatment with HCl gas; yield 5.4 g.; m.p. 172–173°; reported,[12] 175°.

dl-3,4-Dimethyl-α-hydroxy-N-methyl-β-phenethylamine. 3,4-Dimethyl-ω-chloroacetophenone, m.p. 76–77°, was obtained in 84% yield from *o*-xylene, chloracetyl chloride, and anhydrous $AlCl_3$ in carbon disulfide as described by Kunckell.[25] The solid chloroketone (36.5 g.) was added portionwise to a stirred mixture of 150 ml. of alcohol, 25 g. of *N*-methylbenzylamine, and 25 g. of anhydrous Na_2CO_3. The mixture was then heated at gentle reflux and stirred for 6 hr. After filtration from inorganic salts and evaporation of the alcohol, the residue was treated with water, and the insoluble oil extracted with ether. The ether solution was washed with water, dried and distilled; the fraction boiling at 170–175°/0.4 mm. was collected as crude product; yield, 33.6 g. (63%). Conversion to the hydrochloride salt by addition of dry HCl gas to an ether solution of the base gave 29.3 g. (50%) of *3,4-dimethyl-N-benzyl-N-methylaminoacetophenone hydrochloride*, m.p. 197–198° (dec.).

Anal. Calcd. for $C_{18}H_{22}ClNO$: C, 71.2; H, 7.3; Cl, 11.7. Found: C, 70.8; H, 7.2; Cl, 11.6.

A solution of 27.5 g. of the aminoketone hydrochloride in 200 ml. of C.P. methanol was hydrogenated in a Parr apparatus in the presence of 1 g. of 10% palladium-charcoal at room temperature and 3 atm. of hydrogen pressure. The amount of hydrogen absorbed was sufficient for simultaneous hydrogenolysis of the benzyl group and reduction of the carbonyl to hydroxyl. The catalyst was removed by filtration and the solvent distilled off under reduced pressure. The residual oil was finally induced to crystallize by stripping with benzene and finally triturating the residue with ether. The crude product was then recrystallized twice from ethanol-ether to obtain 12.5 g. (65%) of *dl*-3,4-dimethyl-α-hydroxy-*N*-methyl-β-phenethylamine hydrochloride, m.p. 137–138°.

DL-*3,4,5-Trimethyl-α-hydroxy-N-methyl-β-phenethylamine.* 3,4,5-Trimethylacetophenone[26] (60 g.) in 150 ml. of glacial acetic acid was treated with 59 g. of bromine at room temperature. The solution was concentrated to one third its volume and cooled to allow the product to crystallize; yield of *3,4,5-trimethyl-ω-bromoacetophenone*, 47.6 g. (54%); m.p. 77.5–78°, after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{13}BrO$: Br, 33.2. Found: Br, 32.9.

Treatment of 40 g. of the bromoketone with 20.8 g. of *N*-methylbenzylamine and 22 g. of anhydrous Na_2CO_3 in 125 ml. of ethanol as described previously for the 3,4-dimethyl compound and isolation of the product as the HCl salt gave 31.6 g. of *3,4,5-trimethyl-N-benzylmethylaminoacetophenone hydrochloride*, m.p. 178.5–179°, after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{19}H_{24}ClNO$: C, 71.9; H, 7.6; Cl, 11.2. Found: C, 71.9; H, 7.5; Cl, 11.2.

A solution of 26.2 g. of the aminoketone hydrochloride in 150 ml. of C.P. methanol was hydrogenated in a Parr apparatus using an initial hydrogen pressure of 3 atm. in the presence of 1 g. of 10% palladium-charcoal catalyst. Simultaneous debenzylation and reduction of the carbonyl group occurred. The catalyst was removed by filtration and the solvent distilled off under reduced pressure to leave a product which crystallized when triturated with ether; yield of *dl*-3,4,5-trimethyl-α-hydroxy-*N*-methyl-β-phenethylamine hydrochloride, 14.5 g. (76%); m.p. 186–187°.

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Bitter Principles from *Echinocystis Fabacea*[1]

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From ether extracts of the juice of *Echinocystis fabacea*, two crystalline compounds of the apparent molecular formula $C_{30}H_{44}O_8$ have been isolated. One of these compounds is identical with curbitacin B and the other is a new compound which has been named *fabacein*. Both compounds have at least three hydroxyl groups, a readily saponified acetate group, and at least two carbonyl groups, one of which is conjugated with a double bond. Catalytic hydrogenation using a palladium-on-carbon catalyst saturates the carbon-carbon double bond in both compounds. Mild saponification of the hydrogenated compounds yields the same product having the formula $C_{28}H_{44}O_6$. Refluxing the hydrogenated compounds with methanolic alkali gives a compound, $C_{28}H_{42}O_6$, which appears to be a conjugated dienone. These compounds and their derivatives are characterized by the difficulty with which crystalline products can be obtained, and by the ease with which rearrangements apparently take place.

Recent publications on the bitter principles of members of the *Cucurbitaceae*[2] and a revival of interest in elaterin[3] and other compounds obtained from *Ecballium elaterium*,[4] because of their necrotizing action on tumors,[5] has prompted us to report the results of our work thus far on the bitter principles present in another member of the *Cucurbitaceae*, *Echinocystis fabacea*, the common man-root of central coastal California. It has been reported[6] that decoctions of the root of this plant were used by the California Indians to poison fish and to commit suicide, and by their medicine men to poison aged people when they became sick and decrepit. In the native practice of medicine both the seeds and the root were highly valued as a specific against rheumatism and venereal diseases. The root also was said to have a strong cathartic action. It is reported that extracts were used in California to make "Stoughton's Bitters."[7]

Previous work has shown that acid hydrolysis of the juice from the root yields a dark brown insoluble humus-like material from which a crystalline sapogenin, called echinocystic acid, was isolated.[8] Subsequently the structure of this compound was shown to be 16-hydroxyoleanolic acid.[9] Attempts to isolate a pure saponin from the juice have not been successful, but have indicated that the saponin is not responsible for the bitterness of the plant. The latter substances can be obtained directly from the fresh juice of the plant by extraction with chloroform or ether. From ether extracts, three crystalline products and an amorphous fraction have been isolated. The crystalline products are only slightly soluble in water, and the bitter taste is hardly discernible unless one tastes an alcoholic solution of the crystals. The amorphous fraction has the extremely bitter taste of the plant, the disagreeable effect at the back of the tongue and throat being very characteristic.

One of the crystalline compounds, m.p. 201–202°, $[\alpha]_D^{25}$ + 36° in ethanol was named fabacein I, and the other, m.p. 178–179°, $[\alpha]_D^{25}$ + 87° in ethanol, was called fabacein II. The third product, m.p. 230–231°, was called fabacein III.[10] Since then it has been found by paper chromatography that although fabaceins I and II are homogeneous, the material called fabacein III may be a mixture of products or convertible to a mixture of products on standing. Moreover, direct comparison of faba-

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