113. *Some Amines and Amides derived from Vanillin.*

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A number of derivatives of vanillylamine (3-methoxy-4-hydroxybenzylamine) have been prepared including the chaulmoogroyl and sulphanilamides. Other benzylamines and homobenzylamines have been converted into the N^1-benzylsulphanilamides. Vanillinanil has been aminated and the sulphanilamidine prepared. Vanillylidenecyanoacetic ester and its aniline condensation compound were converted by way of the imino-chloride into the corresponding amidine hydrochlorides. All these compounds have been or will be tested biologically; the results so far known are recorded.

[No formulæ are printed for compounds (I)—(XIV). They can be obtained by placing the groups indicated in positions 1, 2, 3, and 4 in the benzene ring (see Table I).]

Vanillylamine (I) was prepared from vanillin oxime by Nelson's method (*J. Amer. Chem. Soc.*, **1919**, **41**, 1118). Condensation of this amine with long-chain fatty acid chlorides gave *amides* of type (II) related to capsaicin (III), which when volatilised had a strong sternutatory action and also produced a hot taste at the back of the throat.

Table I.

Compound.	Position in benzene ring. 1.	2.	3.	4.
I	OH	OMe	H	$CH_2 \cdot NH_2$
II	OH	OMe	H	$CH_2 \cdot NH \cdot CO \cdot$Alk
III	OH	OMe	H	$CH_2 \cdot NH \cdot CO \cdot [CH_2]_4 \cdot CH{:}CMe_2$
IV	$O \cdot C_6H_4 \cdot NO_2(p)$, etc.	OMe	H	$CH_2 \cdot NH \cdot CO \cdot C_5H_{11}$
V	OH	OMe	H	X
VI	OMe	OMe	H	X
VII	OH	OH	H	X
VIII	OMe	H	H	X
IX	OH	H	H	X
X	OH	OEt	H	X
XI	$O \cdot CH_2 \cdot O$		H	X
XII	H	OMe	OH	X
XIII	OH	OMe	H	CH_2X
XIV	OH	OMe	H	$CH_2 \cdot CHMe \cdot NH \cdot SO_2 \cdot C_6H_4 \cdot NH_2$

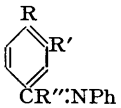
X = $\cdot CH_2 \cdot NH \cdot SO_2 \cdot C_6H_4 \cdot NH_2(p)$.

The chaulmoogroyl *amide* was tested against tuberculosis in mice without result. The *p*-nitrobenzoates and other *esters* (IV) of the hexoyl amide were prepared; their reduced volatility decreased their sternutatory action, but their hot taste increased.

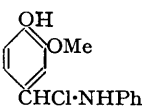
Sulphanilvanillylamide (V) had slight antimalarial activity against *P. gallinaceum* in chicks; accordingly, the *sulphanilbenzylamides* (VI), (VII), (VIII), (IX), (X), (XI), and (XII) were

prepared from the corresponding 4-aldehydes [except (IX), which was prepared from the amine (OH, H, H, $CH_2 \cdot NH_2$) obtained by demethylation of (OMe, H, H, $CH_2 \cdot NH_2$)]. None of these had greater activity than sulphanilvanillylamide. This is surprising in the case of (X) since the parent aldehyde (OH, OEt, H, CHO) has 20 times the taste of vanillin (OH, OMe, H, CHO). Since the corresponding N^1-phenylsulphanilamides which have been prepared do not show any great chemotherapeutical activity (Northey, *Chem. Reviews*, 1940, **27**, 97), the *homobenzylamide* (XIII) was prepared from homovanillin (Harries and Haarmann, *Ber.*, 1915, **48**, 29, 868), and the *compound* (XIV) from the corresponding amine supplied by Dr. J. H. Turnbull in the same way as the lower homologues. The results of the biological tests on these two compounds are not yet to hand.

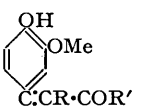
Piperonylideneaniline (XV; RR′ = O·CH_2·O, R″ = H) has been aminated with sodamide in toluene to give a 13% yield of the *amidine* (XV; RR′ = O·CH_2·O, R″ = NH_2) (Kirssanow and Iwastchenko, *Bull. Soc. chim.*, 1935, **2**, 2114, 2121). This method gave only a trace of the amidine (XV; R = OAc or OBz, R′ = OMe, R″ = NH_2) when applied to the vanillinanil derivatives (XV; R = OAc or OBz, R′ = OMe, R″ = H). Prolonged reaction with a solution of sodamide in liquid ammonia at room temperature gave a small yield of the *amidine* (XV; R = OAc, R′ = OMe, R″ = NH_2), which was condensed with *p*-acetylsulphanilyl chloride. The condensation product was hydrolysed under mild conditions with hydrochloric acid (Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1943, **65**, 354) to give the N-*sulphanil*-N^1-*phenylamidine hydrochloride* (XV; R = OH R′ = OMe, R″ = NH·SO_2·C_6H_4·NH_2,HCl) which is undergoing biological tests.



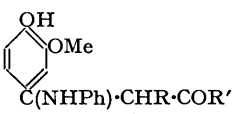
(XV.)



(XVI.)



(XVII.)



(XVIII.)

Vanillinanil was found to form a stable addition *compound* (XVI) with hydrogen chloride, on which ammonia or sodium hydroxide, under various conditions, either had no action or gave the free anil. With sodiocyanoacetic ester the compound gave (XVIII; R = CN, R′ = OEt), identical with the *product* of condensation of aniline and vanillylidenecyanoacetic ester, showing that the addition compound has the expected structure (XVI). The compounds (XVII) and (XVIII) (R = CN, R′ = OEt), under a modification of the conditions used by Pinner (*Ber.*, 1895, **28**, 478) for the conversion of cyanoacetic ester into α-amidinoacetamide hydrochloride, gave the *amidine hydrochlorides* (XVII) and (XVIII) [R = C(:NH)·NH_2,HCl, R′ = NH_2]. Poor yields were obtained in the former case owing to the low reactivity of the cyanide group, most of the starting material being recovered unchanged, and more drastic conditions decreased the yield; in the latter case much tar was formed, but less drastic conditions reduced the yield. The conversion of the ester into an amide took place when the imino-chloride was treated with alcoholic ammonia, and the use of more dilute ammonia to avoid this conversion gave a basic product which would not crystallise. In each case the free amidines were unstable oils which were not investigated further.

Experimental.

(All m. ps. and b. ps. are uncorrected.)

Preparation of Acyl Chlorides.—Thionyl chloride (1·5 equivs.) was added to a chloroform or ether solution of the acid (1 equiv.), the whole heated for 1 hr. on the water-bath, and the solvent and excess of thionyl chloride removed under reduced pressure; the unsaturated acid chlorides could not be distilled.

Preparation of Vanillylamides.—This was carried out as described by Nelson (*J. Amer. Chem. Soc.*, 1919, **41**, 2121) except that the amine was dried for 48 hrs. at 1 mm. in a vacuum desiccator. The hexoyl and undecenoyl vanillylamides agreed in every respect with the compounds described by Nelson (*ibid.*, pp. 2123, 2127).

Oleovanillylamide (cf. II).—Vanillylamine (1 g.) with oleoyl chloride (0·96 g.) gave the *amide* (0·9 g., 66%), which was recrystallised from benzene–petrol; m. p. 36° (Found: N, 3·4. $C_{26}H_{43}O_3N$ requires N, 3·4%).

Ricinoleovanillylamide.—Vanillylamine (1 g.) with ricinoleoyl chloride (1·1 g.) gave the *amide* (1·05 g., 65%), which crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 24° (Found: N, 3·7 $C_{35}H_{43}O_3N$ requires N, 3·5%).

Chaulmoogroyl Chloride.—Chaulmoogric acid (10 g.; m. p. 55°, equiv., 278) was dissolved in light petroleum (b. p. 40—60°, 100 c.c.), and phosphorus trichloride (3 g.) added dropwise with continuous stirring under anhydrous conditions at room temperature. The whole was gently refluxed with stirring for 0·4 hr. When cold, the light petroleum solution was decanted from the phosphoric acid, which

was washed by decantation with light petroleum. The volatile components were removed from the solution and washings under reduced pressure in a water-bath at 45°. The residue (10·6 g.) was used directly since it could not be distilled.

Chaulmoogrovanillylamide.—Vanillylamine (3·0 g. in ether as above) with chaulmoogroyl chloride (3·3 g.) gave the *amide* (3·4 g., 74%) as a colourless waxy solid, becoming cream on standing. Recrystallised from benzene–petrol, it had m. p. 69° (Found: C, 75·0; H, 10·0; N, 3·4. $C_{26}H_{41}O_3N$ requires C, 75·2; H, 9·9; N, 3·4%).

O-*Benzoyl*-N-*hexovanillylamide* (as IV).—To a mixture of benzoyl chloride (0·14 g.) and hexovanillylamide (0·25 g.) was added sodium hydroxide solution (25%) until no further reaction took place. After dilution, the *product* was filtered off; it recrystallised from toluene as a colourless crystalline solid (0·3 g., m. p. 210°) (Found: N, 4·0. $C_{21}H_{25}O_4N$ requires N, 3·95%).

O-p-*Nitrobenzoyl*-N-*hexovanillylamide.*—To *p*-nitrobenzoyl chloride (0·2 g.) in pyridine (2 c.c.) was added hexovanillylamine (0·25 g.). After being heated to 100° for 0·5 hr. and diluted with water, the *product* was collected; it crystallised from toluene in pale yellow needles (0·2 g.), m. p. 235° (Found: N, 7·4. $C_{21}H_{24}O_6N_2$ requires N, 7·0%).

O-2 : 4-*Dinitrobenzoyl*-N-*hexovanillylamide.*—Prepared as for the *p*-nitro-compound but from 2 : 4-dinitrobenzoyl chloride (0·24 g.), this *amide* crystallised from light petroleum (b. p. 100—120°) in yellow needles (0·3 g., m. p. 259°) (Found: N, 9·3. $C_{21}H_{23}O_8N_3$ requires N, 9·2%).

O-3 : 5-*Dinitrobenzoyl*-N-*hexovanillylamide.*—By a similar method, this *amide* was prepared; recrystallised from toluene, it formed yellow needles (0·25 g., m. p. 281°) (Found: N, 9·3%).

O-2 : 4 : 6-*Trinitrobenzoyl*-N-*hexovanillamide.*—Trinitrobenzoyl chloride (0·29 g.) in pyridine (1·4 c.c.) and hexovanillylamide (0·25 g.) were heated to 100° (for 0·25 hr.), the solution diluted, and the *product* recrystallised from toluene. It formed yellow needles (0·1 g., m. p. 296°) (Found: N, 11·7. $C_{21}H_{22}O_{10}N_4$ requires N, 11·45%).

O-5-*Nitrosalicyl*-N-*hexovanillylamide.*—Hexovanillylamide (0·25 g.) was added to 5-nitrosalicyl chloride (0·23 g.) in pyridine (2·2 c.c.) and allowed to stand. After dilution with water, the *product* was recrystallised from toluene, forming very pale yellow needles (0·24 g., m. p. 301°) (Found: N, 6·9. $C_{21}H_{24}O_7N_2$ requires N, 6·7%).

O-*Picryl*-N-*hexovanillylamide.*—Hexovanillylamide (0·25 g.) was added to picryl chloride, and the whole heated to 50° for 0·5 hr. The *product* was recrystallised from alcohol and then from methanol and formed yellow cubes (0·4 g., m. p. 149°) (Found: N, 8·4. $C_{20}H_{22}O_9N_4$ requires N, 8·3%).

The high m. ps. prevented successful volatilisation of the above compounds. The thoroughly dried, finely powdered materials were very irritating to the mucous membrane and had strong, hot tastes.

2-*Chloro*-5-*nitrobenzenesulphonvanillylamide.*—2-Chloro-5-nitrobenzenesulphonyl chloride (2·56 g.) was added to vanillylamine (1·5 g.) in acetone (25 c.c.) and pyridine (5 c.c.), and the whole warmed on the water-bath; after cooling, the *product* was filtered off and recrystallised with some difficulty from alcohol as colourless plates (3·0 g., m. p. 220°) (Found: N, 7·7. $C_{14}H_{13}O_6N_2SCl$ requires N, 7·6%).

Preparation of Oximes.—(1) Aldehydes with a free hydroxyl group (0·1 mol.) were dissolved in water (60 c.c.) containing sodium hydroxide (4·9 g.), and a solution of hydroxylamine hydrochloride (8·6 g.) in water (22 c.c.) was added. The whole was shaken until the precipitated oil solidified. After standing for 12 hrs. in the cold, the solid was filtered off and washed with water. The oximes could be purified with great loss by recrystallisation from toluene, but usually the crude product was used directly in the next stage.

(2) Aldehydes with no free hydroxyl group (0·1 mol.) were dissolved in alcohol (30—40 c.c.) and treated with hydroxylamine hydrochloride as above, followed by sodium hydroxide solution (10%, 45 c.c.) added in portions with shaking. After 3 hrs., a small amount of hydrochloric acid was added, and the precipitate filtered off and washed with water. The crude oxime was usually used directly in the next stage.

Preparation of Amine Hydrochlorides.—The oxime (0·1 mol.) was dissolved in alcohol (50 c.c.) and treated with sodium amalgam (4%, 250 g.) in small portions. The temperature was kept below 60°, and the mixture kept acid by gradual addition of glacial acetic acid (35—40 c.c.), then acidified to Congo-red with hydrochloric acid, and evaporated to dryness on the water-bath under reduced pressure. The residue was extracted with boiling alcohol, and on cooling, the amine hydrochloride crystallised out (*ca.* 0·05—0·06 mol.).

N^4-*Acetylsulphanilamides* (cf. Northey *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 2220).—The amine hydrochloride (0·1 mol.) and water (100—120 c.c.) were efficiently stirred; sodium carbonate (6 g.) was added, followed alternately by *p*-acetamidobenzenesulphonyl chloride (24 g.; *Org. Synth.*, **5**, 3) and sodium hydroxide solution (40%; 7 c.c. for amines without a free hydroxyl group, 10—12 c.c. for those with) in small portions during 20 mins. The whole was stirred a further 20 mins., neutralised, and filtered. A small portion of the precipitate was recrystallised from alcohol or dilute alcohol and analysed.

Sulphanilamides.—The acetyl compound (0·1 mol.) was dissolved in aqueous or aqueous-alcoholic sodium hydroxide solution (8%; 120 c.c. for non-hydroxyl compounds, 160 c.c. for monohydroxy-, and 210 c.c. for dihydroxy-compounds) and heated on the water-bath for 2—3 hrs. The solution was filtered and made just acid to litmus with hydrochloric acid. The precipitate which separated on cooling was collected and dissolved in boiling water; active charcoal (2—3 g.) was added, and the whole refluxed for 10 mins. The solution was filtered, treated with a little ammonia, and then allowed to cool. The sulphanilamides separated in colourless or slightly sandy, well-formed crystals.

The hydrochlorides were obtained either by dissolving the free base in a small quantity of hot water and adding an excess of concentrated hydrochloric acid, or by dissolving the free base in hot alcohol and passing in hydrogen chloride until the solution was strongly acid. In both cases the hydrochlorides separated on cooling.

The m. ps. and analytical data of the compounds are shown in Tables II and III.

TABLE II.

Condensation products of benzylamines and N^4*-acetylsulphanilyl chloride.*

Amine.	Amine, HCl. M. p.	N^4-Acetyl sulphanilamide. M. p.	Analysis. Found (%). C.	H.	Formula.	Required (%). C.	H.
Vanillylamine	decomp.	215°	54·9	5·1	$C_{16}H_{18}O_5N_2S$	54·9	5·1
Veratrylamine	257°	183	56·2	5·5	$C_{17}H_{20}O_5N_2S$	56·0	5·4
3 : 4-Dihydroxybenzylamine	172	175	52·1	4·3	$C_{15}H_{16}O_5N_2S$	52·2	4·35
p-Methoxybenzylamine ...	235	181—182	57·4	5·3	$C_{16}H_{18}O_4N_2S$	57·5	5·3
p-Hydroxybenzylamine ...	195 (HBr)	133	56·3	4·7	$C_{15}H_{16}O_4N_2S$	56·3	5·0
Vanillylethylamine.....	222—223	251 (decomp.)	55·9	5·1	$C_{17}H_{20}O_5N_2S$	56·0	5·4
Piperonylamine	227	181—182	55·4	4·4	$C_{16}H_{16}O_5N_2S$	55·2	4·6
O-Vanillylamine	decomp.	162	54·8	5·2	$C_{16}H_{18}O_5N_2S$	54·9	5·1

TABLE III.

Compound.	*Free base.* M. p.	Analysis. Found (%). C.	H.	Formula.	Required (%). C.	H.	*Hydrochloride.* M. p.	Analysis. Found (%). C.	H.	Required (%). C.	H.
V	*	54·6	5·3	$C_{14}H_{16}O_4N_2S$	54·5	5·2	*	48·8	4·95	48·9	5·0
VI	152—153°	56·2	5·7	$C_{15}H_{18}O_4N_2S$	55·9	5·6	210 *	50·6	5·2	50·2	5·3
VII	*	53·0	5·0	$C_{13}H_{14}O_4N_2S$	53·0	4·75	*	47·1	4·6	47·2	4·7
VIII	131	58·0	5·6	$C_{14}H_{16}O_3N_2S$	57·5	5·5	217	50·9	5·2	51·1	5·2
IX	*	54·0	4·8	$C_{13}H_{14}O_3N_2S$	54·2	4·9	213 *	48·3	4·4	48·1	4·6
X	*	55·7	5·4	$C_{15}H_{18}O_4N_2S$	55·9	5·6	*	50·4	5·3	50·2	5·3
XI	185—186	54·5	4·5	$C_{14}H_{14}O_4N_2S$	54·9	4·7	208—209	49·4	4·5	49·1	4·4
XII	163—164	54·8	5·7	$C_{14}H_{16}O_4N_2S$	54·5	5·2	193—194 *	49·2	5·2	48·9	5·0

* = Decomposes or melts with decomposition.

Sulphanilhomovanillylamide (XIII).—*O*-Acetylhomovanillin (Harries and Haarmann, *loc. cit.*; 20 g.) was refluxed with hydroxylamine hydrochloride (8 g.) and calcium carbonate (12 g.) in methanol (140 c.c.) with vigorous stirring for 3 hrs. The solution was filtered and treated as above with sodium amalgam (4%, 400 g.) and glacial acetic acid (65 c.c.). The *O-acetylhomovanillylamine hydrochloride* recrystallised from alcohol as colourless needles (9 g., m. p. 190° decomp.) (Found: C, 53·7; H, 6·6. $C_{11}H_{15}O_3N$,HCl requires C, 53·8; H, 6·5%). Condensation with acetylsulphanilyl chloride gave N^4*-acetylsulphanilhomovanillylamide* (11 g. crude) which crystallised from alcohol in stout prisms (m. p. 271° decomp.) (Found: C, 55·8; H, 5·1. $C_{17}H_{20}O_5N_2S$ requires C, 56·0; H, 5·4%). Hydrolysis with sodium hydroxide solution (10%, 100 c.c.) containing a little alcohol (5—6 c.c.) at 100° for 2 hrs. removed both acetyl groups to give *sulphanilhomovanillylamide*, which crystallised from water in colourless needles (6 g., m. p. 241° decomp.) (Found: C, 55·9; H, 5·5. $C_{15}H_{18}O_4N_2S$ requires C, 55·9; H, 5·6%). The *hydrochloride* (needles from alcohol) decomposed on heating (Found: C, 50·3; H, 5·6. $C_{15}H_{18}O_4N_2S$,HCl requires C, 50·2; H, 5·3%).

Sulphanil-α-vanillylethylamide. α-Vanillylethylamine (0·9 g., m. p. 157°) was condensed under the same conditions to give N^4*-acetylsulphanil-α-vanillylethylamide* (1·3 g., stout prisms from alcohol, m. p. 293°) (Found: C, 57·3; H, 5·8. $C_{18}H_{22}O_5N_2S$ requires C, 57·2; H, 5·8%). Hydrolysis with sodium hydroxide solution (10%, 5 c.c.) at 100° for 2 hrs. gave *sulphanil-α-vanillylethylamide* (0·9 g., needles from water, m. p. 252°) (Found: C, 57·1; H, 6·0. $C_{16}H_{20}O_4N_2S$ requires C, 57·2; H, 5·95%). The *hydrochloride* (long needles from alcohol) had m. p. 283° (Found: C, 52·9; H, 5·6. $C_{16}H_{20}O_4N_2S$,HCl requires C, 53·0; H, 5·8%).

Sulphanil-O-acetylvanillylamide.—Sulphanilvanillylamide sulphate (7·0 g.) and acetic anhydride (12 c.c.) were vigorously stirred while concentrated sulphuric acid (15 c.c.) was added drop-wise, the whole being maintained below 25°. Absolute alcohol was slowly added to the solution to a final volume of 130 c.c. The precipitate was filtered off, and the *amide sulphate* recrystallised from dilute sulphuric acid as colourless prisms (6·4 g.) (Found: C, 48·7; H, 4·8; N, 9·7. $C_{13}H_{13}O_4N_2,\frac{1}{2}H_2SO_4$ requires C, 48·8, H, 4·9; N, 9·7%). The compound gave no colour with ferric chloride but on diazotisation (Hodgson and Walker, *J.*, 1933, 1621) it coupled with alkaline β-naphthol to give a red product.

O-Acetylvanillinanil.—*O*-Acetylvanillin (9·7 g.) was refluxed with aniline (4·6 g.) in alcohol (50 c.c.) containing a trace of piperidine for 4 hrs. The alcohol was distilled off, and the residue poured into water. The precipitate was filtered off, washed with water, and recrystallised from dilute alcohol, forming glistening plates (13 g.), m. p. 85—86° (Found: C, 71·5; H, 5·7. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

O-Benzoylvanillinanil, prepared as above from *O*-benzoylvanillin, or by a Schotten–Baumann benzoylation of vanillinanil, crystallised from dilute alcohol in glistening plates, m. p. 157—158° (Found: C, 76·1; H, 5·2. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·1%).

O-Acetylvanill-N^1*-phenylamidine* (XV; R = OH, R′ = OMe, R″ = NH_2).—(1) Finely powdered sodamide (12 g.) was added to acetylvanillinanil (20 g.) in dry benzene (30 c.c.). The whole was stirred under anhydrous conditions and warmed in a bath at 85° (which was temporarily removed if frothing

became too violent) for 1 hr. Crushed ice (150 g.) was added to the cold pale green mass, the whole vigorously shaken, and acidified with dilute hydrochloric acid. The precipitate was filtered off and the filtrate boiled with a little active charcoal, refiltered, and evaporated to dryness. The residue was extracted with hot alcohol and the extract was concentrated, and the material deposited on cooling was recrystallised from alcohol, forming pale prisms (0·1 g.), m. p. 230° (decomp.). These were dissolved in a little water, and the solution basified and extracted with ether. The extract was dried, evaporated, and the residual ***amidine*** recrystallised from benzene–petrol, forming stout colourless prisms, m. p. 116° (Found : C, 67·1; H, 5·5. $C_{16}H_{16}O_3N_2$ requires C, 67·6; H, 5·6%).

(2) Powdered sodium (3 g.) was dissolved in liquid ammonia (200 c.c.) and acetylvanillinanil (10 g.) added. The whole was sealed in a stout tube and shaken at room temperature for 72 hrs. The ammonia was allowed to evaporate, a mixture of hydrochloric acid (25 c.c.) and crushed ice (150 g.) added, the whole shaken, and allowed to stand. The solution was filtered and evaporated to dryness, the residue extracted with hot alcohol, the alcohol removed, and the residue taken up in water (20 c.c.). The aqueous solution was boiled with a little active charcoal, filtered, and evaporated to dryness; the residue crystallised from alcohol in pale prisms (0·8 g.), m. p. 230° (decomp.), identical with the amidine hydrochloride above.

In both methods (1) and (2) the amidine was obtained directly by working up as described by Kirssanow and Iwastchenko (*locc. cit.*) and recrystallised from benzene–petrol; colourless plates, m. p. 119° [0·01 g. for method (1) and 0·2 g. for method (2)] (Found : C, 67·8; H, 5·6%).

O-*Benzoylvanill*-N^1-*phenylamidine*.—(1) Benzoylvanillinanil (22 g.), treated with sodamide as above, gave the amidine hydrochloride, which crystallised from alcohol in colourless plates (0·03 g.), m. p. 254° (decomp.). (2) Benzoylvanillinanil (11 g.) when aminated in liquid ammonia as above gave the *amidine hydrochloride* (0·9 g.), m. p. 245° (decomp.) (Found : C, 65·8; H, 4·4. $C_{21}H_{18}O_3N_2$,HCl requires C, 65·9; H, 4·6%).

The *amidine* was obtained by the alternative method of working up described above, or by dissolving the hydrochloride (0·5 g.) in water (4 c.c.), basifying the solution, and extracting it with ether. The extract was dried, the ether removed, and the residue recrystallised from benzene–petrol, forming colourless plates, m. p. 131° (Found : C, 71·0; H, 5·3. $C_{21}H_{18}O_3N_2$ requires C, 70·8; H, 5·05%).

N^4-*Acetylsulphanilyl*-O-*acetylvanill*-N^1-*phenylamidine*.—*O*-Acetylvanill-N^1-phenylamidine hydrochloride (0·5 g.) was dissolved in water, and sodium carbonate (0·2 g.) added, followed by *p*-acetamidosulphanilyl chloride (0·5 g.) and sodium hydroxide solution (10%, 0·8 g.) alternately in small portions at 40° with stirring. After 0·5 hr. the reaction mixture was allowed to cool, and the condensation *product* filtered off and recrystallised from alcohol (0·6 g. of colourless prisms, m. p. 180°) (Found : C, 59·1; H, 5·1. $C_{23}H_{23}O_6N_3S$ requires C, 58·8; H, 4·9%).

Sulphanilylvanill-N^1-*phenylamidine*.—The above diacetyl compound (0·5 g.) was suspended in alcoholic hydrogen chloride (20%, 20 c.c.) containing concentrated hydrochloric acid (0·5 c.c.). The whole was shaken at room temperature for 36 hrs., and the hydrochloride filtered off and recrystallised from dilute hydrochloric acid; stout needles (0·3 g., decomp. 222°) (Found : C, 55·4; H, 4·3. $C_{20}H_{19}O_4N_3S$,HCl requires C, 55·4; H, 4·4%). The hydrochloride was dissolved in water and the solution neutralised. The *amidine* was collected and recrystallised from dilute alcohol, forming colourless prisms, m. p. 150—152° (Found : C, 65·7; H, 5·0. $C_{20}H_{19}O_4N_3S$ requires C, 65·8; H, 5·1%).

Phenyl-α-chloro-4-hydroxy-3-methoxybenzylamine ("*Vanillinanil Hydrochloride*") (XVI).—(1) Vanillinanil (20 g.) was dissolved in hot alcohol (60 c.c.) and added to warm dilute hydrochloric acid (15%, 120 c.c.). On cooling, the solution gave large yellow cubes of the addition *compound* (20·5 g., m. p. 132°) (Found : Cl, 13·2. $C_{14}H_{14}O_2NCl$ requires Cl, 13·4%). (2) Vanillinanil (20 g.) was dissolved in warm alcohol (100 c.c.), and the solution saturated with hydrogen chloride at 50—60°. On cooling, small green crystals were formed (14 g., m. p. 206°) (Found : Cl, 13·3%). The yellow form was the more stable below 130°, and the green form the more stable above. If the yellow form was melted and the temperature of the bath maintained, the compound re-solidified to the green form; a mixture of the two forms softened slightly at 130°, but melted at 205°.

α-Amidinoacetamide Hydrochloride.—A mixture of cyanoacetic ester (10 g.) and alcohol (10 c.c.) was saturated at — 20° with dry hydrogen chloride, sealed in a stout tube, and kept at 40° for 30 hrs. The volatile components were removed in a vacuum, and the solid colourless residue shaken with ice-cold saturated alcoholic ammonia (250 c.c.). The solution was refluxed for 0·5 hr., concentrated, and filtered. The hot filtrate was acidified with hydrogen chloride and allowed to cool. The crystalline precipitate recrystallised from alcohol or water in colourless prisms (6 g., decomp. 162—163°) (Found : C, 26·6; H, 5·6. Calc. for $C_3H_8ON_3Cl$: C, 26·2; H, 5·8%).

α-Amidino-α-vanillylideneacetamide Hydrochloride [XVII; R = C(:NH)·NH_2, R′ = NH_2].—Vanillylidenecyanoacetic ester (Lapworth and Wykes, *J.*, 1917, **111**, 796; 8 g.) was dissolved in dry alcohol (160 c.c.) and saturated at — 20° with dry hydrogen chloride. The solution, sealed in a stout tube, was allowed to stand for 10 days. The volatile components were removed in a vacuum, and the residue shaken with cold saturated alcoholic ammonia (300 c.c.). After standing for 12 hrs., the solution was refluxed for 0·5 hr., concentrated, and filtered. The hot filtrate was acidified with hydrogen chloride and poured into cold water (500 c.c.). The whole was filtered, the filtrate refluxed with a little active charcoal, refiltered, and evaporated to dryness under reduced pressure on a water-bath. The residue was extracted with hot alcohol, the extract concentrated, and allowed to cool. The precipitate recrystallised from water in very pale green prisms (0·3 g., decomp. 151°) (Found : C, 45·5; H, 5·0. $C_{11}H_{13}O_3N_3$,HCl,H_2O requires C, 45·6; H, 5·2%).

Anilinovanillylcyanoacetic Ester (XVIII; R = CN, R′ = OEt).—(1) Cyanoacetic ester (3·5 g.) was refluxed with powdered sodium (0·4 g.) in pure dry benzene (50 c.c.) until no further reaction occurred. Vanillinanil hydrochloride (2 g.) was added in small portions with stirring, and the whole heated on the water-bath for 2·5 hrs. Water (100 c.c.) was added, the solution acidified, and extracted with ether. The extract was washed with water and dried (sodium sulphate), and the solvent removed. The residue recrystallised from dilute alcohol, giving yellow prisms (0·7 g., m. p. 101°) (Found : C, 67·0; H, 5·7. $C_{19}H_{20}O_4N_2$ requires C, 67·1; H, 5·9%).

(2) Vanillylidenecyanoacetic ester (10 g.) and aniline (6 g.) were sealed in a tube with a trace of piperidine acetate and heated at 100° for 48 hrs. The whole was poured into water and worked up as in (1), giving yellow prisms (3 g.), m. p. 101°.

β-Anilino-α-amidino-β-3-methoxy-4-hydroxyphenylpropionamide Hydrochloride [XVIII; R = C(:NH)·NH_2, R′ = NH_2].—The above ester (10 g.) was dissolved in a mixture of dry alcohol (5 c.c.) and dry dioxan (100 c.c.). The solution was saturated with dry hydrogen chloride at — 20° and kept for 20 days in a sealed tube. The volatile components were removed in a vacuum, and the residue shaken with cold saturated alcoholic ammonia (400 c.c.) and allowed to stand for 12 hrs. The solution was refluxed for 0·5 hr., concentrated, and filtered, and the hot filtrate acidified with hydrogen chloride. The whole was poured into water, filtered, the filtrate refluxed with a little active charcoal, and again filtered. The solution was evaporated to dryness under reduced pressure on the water-bath, the residue extracted with hot water, and the extract allowed to cool. The precipitated *amidine hydrochloride* was recrystallised from dilute alcohol, giving yellow prisms (1·2 g.), m. p. 135° (decomp.) (Found : C, 51·5; H, 6·1. $C_{17}H_{19}O_3N_4$,HCl,$2H_2O$ requires C, 51·1; H, 5·8%).

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