TABLE IV

| Compd. | Steroid | 17β-Ester | M.p., °C. | Formula | % calcd. C | % calcd. H | % found C | % found H |
|---|---|---|---|---|---|---|---|---|
| I | Testosterone | 17β-Adamantoate | 217–220 | $C_{30}H_{42}O_3$ | 79.95 | 9.39 | 79.73 | 9.44 |
| II | 4-Chlorotestosterone | 17β-Adamantoate | 304–306 | $C_{30}H_{41}ClO_3$ | 74.27 | 8.51 | 74.31 | 8.59 |
| III | Testosterone | 3-Methyl-17β-adamantoate | 168–170 | $C_{31}H_{44}O_3$ | 80.13 | 9.55 | 79.55 | 9.96 |
| | 4-Bromotestosterone | 17β-Adamantoate | 222–224 | $C_{30}H_{41}BrO_3$ | 68.04 | 7.80 | 68.85 | 8.04 |
| | $\Delta^1$-Androsten-(5α)-17β-ol-3-one | 17β-Adamantoate | 216–219 | $C_{30}H_{42}O_3$ | 79.95 | 9.39 | 79.50 | 9.40 |
| IV | 2α-Methyl-5α-androstan-17β-ol-3-one | 17β-Adamantoate | 223–226 | $C_{31}H_{46}O_3$ | 79.78 | 9.94 | 79.84 | 9.85 |
| V | 2α-Methyl-5α-androstan-17β-ol-3-one | 3-Methyl-17β-adamantoate | 209–211 | $C_{32}H_{48}O_3$ | 79.95 | 10.07 | 80.13 | 10.35 |
| VI | 19-Nortestosterone | 17β-Adamantoate | 203–206 | $C_{29}H_{40}O_3$ | 79.77 | 9.23 | 79.65 | 9.30 |
| VII | 19-Nortestosterone | 3-Methyl-17β-adamantoate | 159–161 | $C_{30}H_{42}O_3$ | 79.95 | 9.39 | 79.83 | 9.40 |
| VIII | 19-Nortestosterone | 3,5-Dimethyl-17β-adamantoate | 132–134 | $C_{31}H_{44}O_3$ | 80.12 | 9.54 | 80.35 | 9.65 |
| IX | 4-Chloro-19-nortestosterone | 17β-Adamantoate | 265–267 | $C_{29}H_{39}ClO_3$ | 73.94 | 8.34 | 73.90 | 8.51 |

tion was allowed to reflux for 18 hr. After cooling, 100 ml. of chloroform and 50 ml. of water were added. The layers were separated, and the organic layer was extracted successively with water, 1% aqueous HCl, and water, and then dried ($Na_2SO_4$). Evaporation of the organic solvent yielded a residue which upon trituration with ether gave crystalline material (1.8 g.), m.p. 244–247°. Recrystallization from ether several times afforded the analytical sample, m.p. 265–267° dec., $[\alpha]^{25}D$ +66.55°.

**Hydrolysis. A.**—To 200 mg. of 19-nortestosterone 17β-cyclohexylcarboxylate dissolved in 20 ml. of methanol was added a solution of 0.2 g. of KOH in 0.5 ml. of water. After being allowed to reflux for 2 hr., the solution was cooled and then neutralized with glacial acetic acid. Water (20 ml.) was added, and the solution was extracted with three 100-ml. portions of ether. The combined ether solution was washed successively with dilute $Na_2CO_3$ solution and water, and was then dried ($Na_2SO_4$). Evaporation of the solvent afforded 162 mg. of a viscous residue which slowly crystallized. Thin layer chromatography (silica gel; chloroform–ether, 1:1) indicated the presence of 19-nortestosterone and the absence of 17β-ester.

**B.**—When 200 mg. of 19-nortestosterone 17β-adamantoate (VI) was treated in the identical manner as above, there was recovered, upon addition of the water, crystalline ester (190 mg.), m.p. 203–205°.

19-Nortestosterone 17β-adamantoate (200 mg.) in 20 ml. of methanol was treated with 2 g. of KOH in 1 ml. of water, and the solution was refluxed for 2 hr. Cooling, neutralization, and the addition of 20 ml. of water precipitated 105 mg. of ester, m.p. 193–197°. The filtrate was evaporated to a smaller volume to remove methanol, and the solution was then extracted with ether. The organic solution was washed with salt solution, dried ($Na_2SO_4$), and evaporated to a viscous residue (100 mg.). Thin layer chromatography showed that this residue consisted of 19-nortestosterone and some unhydrolyzed ester.

**Acknowledgment.**—The authors wish to express their gratitude to Mr. E. Krumkalns for stimulating discussions as well as for supplies of the adamantoic acid chlorides.

# Synthesis of α-(p-Aminophenyl)- and α-(p-Chlorophenyl)-β-arylpropionitriles by Catalytic Reduction of Stilbenenitriles

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Hydrogenation of α-(p-nitrophenyl)-β-arylacrylonitriles in the presence of palladium–charcoal in ethyl acetate solution gives α-(p-aminophenyl)-β-arylpropionitriles. The bearing of some of the results in this work upon earlier reductive cyclization of o-nitrophenylacetonitriles is discussed. Two compounds, α-(p-aminophenyl)-β-(3-pyridyl)propionitrile and the similarly prepared α-(p-chlorophenyl)-β-(3-pyridyl)propionitrile, affect adrenal cortical steroid secretion.

The 1,1-diaryl- and 1,2-diarylethylenes and -ethanes, notably stilbestrol and its relatives, have been of interest in endocrinology for some time.[1] Recently the field was given some new impetus by studies of adrenocortically active, similar basic ketones, the amphenones,[2–7] amphenone-related pyridyl ketones (*e.g.*, metyrapone and relatives),[8–10] and aminoindenes.[6] There also have been recent further studies of the well-known, weakly estrogenic stilbenenitriles[11] in the di-

(1) J. A. Hogg and J. Korman in "Medicinal Chemistry," Vol. 2, F. F. Blicke and C. M. Suter, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 2.

(2) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114, 117 (1950).

(3) W. L. Bencze and M. J. Allen, *J. Org. Chem.*, **22**, 352 (1957).

(4) W. L. Bencze, L. I. Barsky, M. J. Allen, and E. Schlittler, *Helv. Chim. Acta*, **41**, 882 (1958).

(5) J. B. Wright and E. S. Gutsell, *J. Am. Chem. Soc.*, **81**, 5193 (1959); J. B. Wright, U. S. Patent 2,881,216 (1959).

(6) W. L. Bencze and M. J. Allen, *J. Med. Pharm. Chem.*, **1**, 395 (1959).

(7) J. J. Chart and H. Sheppard, *ibid.*, **1**, 407 (1959).

(8) W. L. Bencze and M. J. Allen, *J. Am. Chem. Soc.*, **81**, 4015 (1959).

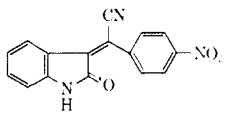
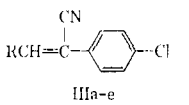
(9) W. L. Bencze, C. A. Burckhardt, and W. F. Yost, *J. Org. Chem.*, **27**, 2865 (1962).

(10) J. J. Chart, H. Sheppard, M. J. Allen, W. L. Bencze, and R. Gaunt, *Experientia*, **14**, 151 (1958).

(11) J. B. Niederl and A. Ziering, *J. Am. Chem. Soc.*, **64**, 885 (1942); see also S. Wawzonek, *ibid.*, **68**, 1157 (1946).

TABLE I

*p*-NITRO- AND *p*-CHLOROSTILBENENITRILES

| Compd. | R | M.p., °C. | Color | Yield, % | Lit. ref. | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| |  Ia–g | | | | | | | | | | |
| Ia | 2-Pyridyl | 200–201.5 | Pale yellow | 99 | ... | 66.92 | 3.61 | 16.73 | 66.68 | 3.57 | 16.70 |
| b | 3-Pyridyl | 156–157 | Pale yellow | 88 | 17 | ... | ... | ... | ... | ... | ... |
| c | 4-Pyridyl | 156–157 | Greenish yellow | 81 | ... | 66.92 | 3.61 | 16.73 | 67.24 | 3.94 | 16.49 |
| d | *m*-Nitrophenyl | 197–198 | Pale yellow | 97 | 20–23 | ... | ... | ... | ... | ... | ... |
| e | *p*-Nitrophenyl | 211–213 | Light orange | 74 | 23, 25 | ... | ... | ... | ... | ... | ... |
| f | *p*-Dimethylaminophenyl | 243–244 | Red-purple | 83 | 24, 25 | ... | ... | ... | ... | ... | ... |
| g | *p*-Chlorophenyl | 184–186 | Yellow | 97 | 23 | ... | ... | ... | ... | ... | ... |
| h | 2,4-Dichlorophenyl | 180–181 | Pale yellow | 87 | ... | 56.45 | 2.53 | 8.78 | 56.39 | 2.57 | 8.48 |
| i | *m*-Hydroxyphenyl | 235–237 dec. | Yellow | 87 | ... | See experimental | | | | | |
| j | *p*-Hydroxyphenyl | *Ca.* 201 dec. | Red-brown | 100 | ... | 67.66 | 3.79 | 10.52 | 67.62 | 4.03 | 11.48 |
| k | 3-Methoxy-4-hydroxyphenyl | 177–180 dec. | Red-purple | 100 | ... | 64.86 | 4.08 | 9.46 | 64.74 | 5.03 | 10.20 |
| l | 3,4-Dimethoxyphenyl | 181–183 | Bright yellow | 94 | ... | 65.80 | 4.55 | 9.03 | 66.17 | 4.65 | 8.70 |
| m | 3,4,5-Trimethoxyphenyl | 169–170 | Orange | 22 | ... | 63.52 | 4.74 | 8.23 | 63.05 | 4.89 | 7.92 |
| n | 3-Indolyl | 261–263 | Orange | 92 | ... | 70.58 | 3.83 | 14.53 | 70.10 | 3.86 | 14.78 |
| |  II | | | | | | | | | | |
| II | | 226–228 dec. | Red | 86 | 25 | ... | ... | ... | ... | ... | ... |
| |  IIIa–e | | | | | | | | | | |
| IIIa | 3-Pyridyl | 137–138.5 | Very pale yellow | 76 | 15 | ... | ... | ... | ... | ... | ... |
| b | *o*-Chlorophenyl | 121–123 | Colorless | 39 | ... | 65.71 | 3.31 | 5.11 | 65.80 | 3.38 | 4.86 |
| c | 2,4-Dichlorophenyl | 182–183 | Pale yellow | 45 | ... | 58.38 | 2.61 | 4.54 | 58.58 | 2.68 | 4.50 |
| d | *p*-Dimethylaminophenyl | 191–192.5 | Bright yellow | 74 | ... | 72.20 | 5.35 | 9.91 | 71.78 | 5.27 | 10.13 |
| e | 3-Indolyl | 210–211 | Bright yellow | 93 | ... | 73.25 | 3.98 | 10.05 | 73.67 | 4.04 | 10.04 |

rection of new diarylethylenes,[12,13] triarylethylenes,[14] and stilbazoles analogous to these substances.[15–17]

The compounds forming the subject of this paper were synthesized in 1958, with the initial idea that basic (aminophenyl and/or pyridyl) analogs of diarylpropionitriles, incorporating in one molecule several structural items from above-mentioned compounds, should also have some effect on the adrenals or gonads.

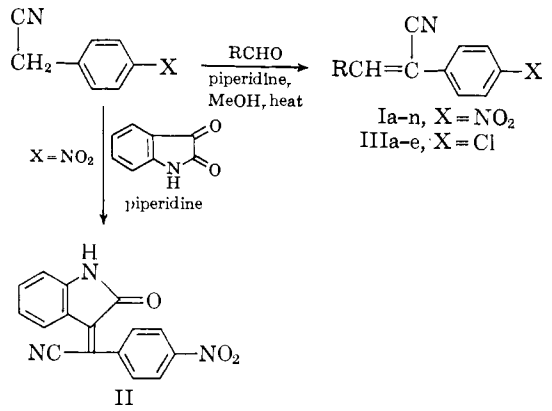
Preparation of $\alpha,\beta$-diarylacrylonitriles by condensation of aldehydes with phenylacetonitriles, although sometimes referred to as an example of the Knoevenagel condensation,[15,18] actually originated with Meyer and Frost[19] and, with nitro compounds, was investigated at an early date by Remse[20] and Freund.[21] The reaction typically is carried out in the presence of a sodium alkoxide,[11,15,17,19–24] although nitriles having sufficiently reactive $\alpha$-methylene groups can be condensed with aldehydes in the presence of organic bases such as piperidine[18,22,25,26] or Triton B,[27] or even without added catalysts when one or both of the reactants is itself sufficiently basic to promote initial carbanion formation.[28] The same general considerations apply to condensation of aldehydes with *p*-nitro-activated phenylacetic acids,[17] in which, however, with piperidine, initially formed $\alpha$-arylcinnamic acids are not isolated but are decarboxylated, giving *trans*-stilbenes.[22,29]

A preliminary experiment, in which pyridine-3-aldehyde was condensed with *p*-nitrophenylacetic acid in the presence of piperidine, gave 1-(3-pyridyl)-2-(*p*-nitrophenyl)ethylene, a result agreeing with the last-mentioned observation.

For the condensation of *p*-nitrophenylacetonitrile with a series of aromatic and heterocyclic aldehydes and isatin, piperidine was chosen to be used as the basic agent, and methanol served as the solvent. The products I and II so obtained, listed in Table I, were isolated very easily, usually in good yields. The same

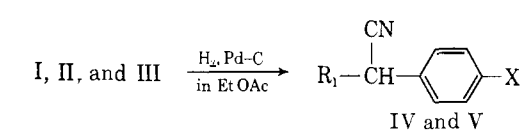
(12) K. J. Rorig, U. S. Patent 2,815,363 (1957).
(13) J. H. Burckhalter, J. Sam, and L. A. R. Hall, *ibid.*, **81**, 394 (1959); J. H. Burckhalter and P. Kurath, *ibid.*, **81**, 395 (1959).
(14) M. G. Van Campen, R. E. Allen, F. P. Palopoli, and E. L. Schumann, Deutsches Auslegeschrift 1,026,744 (1958).
(15) R. N. Castle and W. S. Seese, *J. Org. Chem.*, **20**, 987 (1955).
(16) Ng. Ph. Buu-Hoï, R. Huls, and N. D. Xuong, *ibid.*, **20**, 1407 (1955).
(17) F. H. Clarke, G. A. Felock, G. B. Silverman, and C. M. Watnick, *ibid.*, **27**, 533 (1962).
(18) A. M. Mattocks and O. S. Hutchinson, *J. Am. Chem. Soc.*, **70**, 3516 (1948).
(19) V. Meyer and H. V. Frost, *Ann.*, **250**, 124, 156 (1889).
(20) P. Remse, *Ber.*, **23**, 3133 (1890).
(21) M. Freund, *ibid.*, **34**, 3104 (1901).
(22) H. A. Harrison and H. Wood, *J. Chem. Soc.*, 1195 (1926).
(23) R. v. Walther and A. Wetzlich, *J. prakt. Chem.*, [2] **61**, 169 (1899); R. v. Walther and Raetze, *ibid.*, [2] **65**, 282 (1903).
(24) P. Pfeiffer, *Ann.*, **465**, 20 (1928); see also F. Sachs and W. Lewin, *Ber.*, **35**, 3569 (1902).
(25) R. Merckx, *Bull. soc. chim. Belges*, **58**, 460 (1949); see *Chem. Abstr.*, **45**, 579 (1951); see also W. E. Solodar and M. Green, *J. Org. Chem.*, **23**, 103 (1958).
(26) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955); **78**, 3698 (1956).
(27) W. Herz and J. Brasch, *J. Org. Chem.*, **23**, 711 (1958).
(28) W. Baker, K. M. Buggle, J. F. W. McOmie, and D. A. M. Watkins, *J. Chem. Soc.*, 3594 (1958).
(29) See D. Jambotkar and R. Ketcham, *J. Org. Chem.*, **28**, 2182 (1963).

set of conditions predictably failed to promote condensation between *p*-nitrophenylacetonitrile and aromatic ketones (acetophenone, 3-acetylpyridine), although with a longer reaction period at 100° piperidine could also be used in the condensation of aldehydes with the less reactive *p*-chlorophenylacetonitrile.[15,23] Examples of some products III from this reaction are also included in Table I.




Although nitrostilbenenitriles in the past have been reduced by means of metal and acid to aminostilbenes,[21] and other stilbenenitriles have been hydrogenated catalytically to β,γ-diarylpropylamines,[18] the purpose of the present work was neither of these but rather to reduce nitro to amino groups and to saturate the ethylene bond, preferably in one operation, without affecting the nitrile, which then later presumably could be transformed into other functional groups.

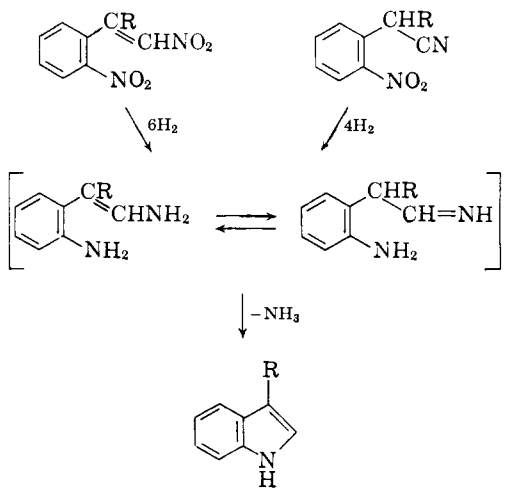
Hydrogenation of the α-(*p*-nitrophenyl)cinnamonitriles presented no difficulty when carried out according to a procedure used earlier[26] in the reduction of *o*-nitrophenylacetonitriles to indoles, *i.e.*, using 10% palladium–charcoal, ethyl acetate as preferred solvent, and 3–4 atm. of hydrogen pressure. The rapid rate of initial hydrogen consumption (3 equiv./nitro group) indicated that, as in earlier work,[21,26] the first attack was upon the nitro groups(s). Past the point of formation of the amino groups, the hydrogenations then proceeded further with saturation of the double bond, and it was observed that this stage was slower[30] and generally required some heat for completion. The total hydrogen absorbed usually exceeded expectation, even when an estimated allowance was made for various experimental errors. Provided that the seemingly excessive uptake was *not* interrupted but allowed to go until it finally became quite slow at 70–80°, fairly good yields of the hitherto unavailable α-(*p*-aminophenyl)propionitriles (IV), listed in Table II, were obtained.




IVa–l, X = $NH_2$; $R_1$ = substituted benzyl, 3-indolylmethyl
IVm, X = $NH_2$; $R_1$ = 3-oxindolyl
V, X = Cl; $R_1$ = 3-pyridyl

The tendency toward over-reduction of many of these amino compounds, as well as the *p*-chlorophenyl compound V, was especially noticeable in the compounds incorporating basic $R_1$ groups. With Ia and Ib this might possibly now be attributed at least partly to slow reduction of pyridine to piperidine.[31] However, since observed in other (nonpyridine) examples as well, it more probably reflects the appreciable rate at which phenylacetonitriles take up hydrogen in the presence of palladium, as they also do even more readily with other catalysts such as nickel and platinum. Two additional, closely related cases, better illustrating the rather surprising ease with which alkylidene- and arylidenephenylacetonitriles may be reduced in the presence of palladium, not only at the double bond but also at the nitrile group, have been observed in this laboratory and may be mentioned in this connection. Cyclopentylidenephenylacetonitrile[32] in ethyl acetate absorbs very rapidly about 3 equiv. of hydrogen in the presence of 10% palladium–charcoal,[33] giving a mixture of basic and nonbasic compounds; α-(3,4-dimethoxyphenyl)-β-phenylacrylonitrile under the same conditions also has a strong tendency to overabsorb, giving ill-defined, nonnitrogenous material as well as α-(3,4-dimethoxyphenyl)-β-phenylpropionitrile which can be prepared thus in good yield if the procedure is used circumspectly.

These findings are of special interest in regard to the unsettled question concerning the way in which *o*-nitro- (*via* *o*-amino-) phenylacetonitriles are converted to indoles under the same[26,34] conditions, or in the presence of Raney nickel.[35] This question essentially has been whether, in an *o*-aminophenylacetonitrile, the amino and cyano groups interact before or after further attack on the molecule by hydrogen. It now seems quite clear that palladium hydrogenation of ArCH(CN)R is related to the better known, abnormal hydrogenation of ω-nitrostyrenes (*o*-nitro derivatives of which also provide indoles[36]), phenylacetoximes, and similar compounds which may lead ultimately to loss of nitrogen through facile hydrolysis, or reaction with a sterically proximate group, of an unstable (aminostyrene, *i.e.*, phenylacetimine) enamine intermediate.




(30) This effect may be attributed to inhibition of the catalyst by newly formed basic moieties, or to the usual slight or moderate difficulty of reducing a diarylethylene, or to a combination of these factors.

(31) G. N. Walker, *J. Org. Chem.*, **27**, 2966 (1962).

(32) M. Jackman, C. Bohlen, F. C. Nachod, B. F. Tullar, and S. Archer, *J. Am. Chem. Soc.*, **71**, 2301 (1949).

(33) This observation was made by Mr. R. T. Smith.

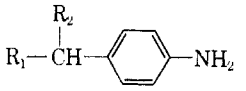
(34) H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.*, **80**, 4622 (1958).

(35) H. Plieninger and I. Nogradi, *Ber.*, **88**, 1961 (1955).

(36) C. F. Huebner, H. A. Troxell, and D. C. Schroeder, *J. Am. Chem Soc.*, **75**, 5887 (1953).

TABLE II

α-(*p*-AMINOPHENYL)PROPIONITRILES AND -PROPIONIC ACIDS



IVa–m

| Compd. | $R_1$ | Compd. reduced; approx. $H_2$ uptake (molar equiv.)[a] | $R_2$ | M.p., °C. | Yield, % | Recrystn. solvent[b] | Calcd., % C | Calcd., % H | Calcd., % N | Found, % C | Found, % H | Found, % N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IVa | 3-Pyridyl-$CH_2$ | Ib; 5.5 | CN | 99–100 | 66 | A | 75.31 | 5.87 | 18.82 | 75.04 | 5.96 | 18.90 |
| | | | COOH | 181–183 | 63 | C | 69.40 | 5.83 | 11.56 | 69.43 | 5.78 | 11.78 |
| b | 4-Pyridyl-$CH_2$ | Ic; 4.2 | CN | 80–84 | | X | | | | | | |
| | | | COOH | 196–198 | 27 | C | 69.40 | 5.83 | 11.56 | 69.84 | 6.03 | 12.2 |
| c | *m*-Aminobenzyl | Id; ca. 9 | CN | Not crystalline | | X | | | | | | |
| | | | COOH | 181–183 | 43 | C D | 70.29 | 6.29 | 10.93 | 70.57 | 6.11 | 10.69 |
| d | *p*-Aminobenzyl | Ie; 8.7 | CN | 95–96 | 95; as ·2HCl | A | 75.92 | 6.37 | 17.71 | 75.77 | 6.37 | 18.04 |
| | | | CN·2HCl | Ca. 250 dec. | | D | 58.07 | 5.53 | 13.54 | 58.49 | 5.70 | 13.56 |
| e | *p*-Dimethylaminobenzyl | If; 5.8 | CN | 140–142 | 70 | B | 76.94 | 7.22 | 15.84 | 77.75 | 7.47 | 16.06 |
| f | *p*-Chlorobenzyl | Ig; 5.5 | CN | 157–159 | 63 | A | 70.17 | 5.10 | 10.91 | 70.35 | 5.03 | 11.09 |
| | | | COOH·HCl | 240–243 dec. | ... | C | 65.34 | 5.12 | 5.08 | 64.96 | 6.73 | 5.21 |
| g | *m*-Hydroxybenzyl | Ii; 4.4 | CN | Not crystalline | | X | | | | | | |
| | | | COOH | 211–214 dec. | 46 | C | 70.02 | 5.88 | 5.44 | 69.84 | 6.09 | 5.64 |
| h | *p*-Hydroxybenzyl | Ij; 4.0 | CN | 158–160 | 90 | AX | 75.60 | 5.92 | 11.76 | 75.86 | 5.97 | 11.86 |
| i | 3-Methoxy-4-hydroxybenzyl | Ik; 3.75 | CN | 160–162 | 95 | BX | 71.62 | 6.01 | 10.44 | 71.42 | 5.79 | 10.44 |
| j | 3,4-Dimethoxybenzyl | Il; 4.8 | CN | 114–116 | 69 | B | 72.32 | 6.43 | 9.92 | 72.10 | 6.34 | 10.10 |
| k | 3,4,5-Trimethoxybenzyl | Im; 4.8 | CN | 161.5–163 | 79 | B | 69.21 | 6.45 | 8.97 | 68.81 | 6.60 | 9.36 |
| l | 3-Indolyl-$CH_2$ | In; 4.5 | CN | 125–127 | 69 | E | 78.13 | 5.79 | 16.08 | 78.21 | 6.04 | 16.37 |
| m | 3-Oxindolyl | II; 4.15 | CN | 215–218 dec. | 55 | C | 72.98 | 4.98 | 15.96 | 72.56 | 5.15 | 16.03 |

[a] See Experimental part. [b] A, cyclohexane–ethyl acetate; B, ethyl acetate; C, methanol; D, water; E, benzene; X denotes those cases in which the aminonitrile was difficult or impossible to obtain in pure form in the presence of solvents because of poor crystalline properties or air discoloration.

Thus the sequence of events (*via* an *o*-aminophenylacetimine) outlined by Snyder[34] in his interpretation of the formation of indoles through further hydrogenation of *o*-aminophenylacetonitriles is almost certain to be the correct one, and the earlier postulated route *via* 2-aminoindolenines[26] may be discarded. Even though 2-aminoindolenines were isolated[26] in some instances after such hydrogenations, these probably are not intermediates for the further formation of indoles and ammonia but were present in the end only in cases where the nitrile group had for one reason or another partially or completely escaped reduction in the presence of the palladium, throughout the hydrogenation process.

It was found difficult to hydrolyze directly some of the aminonitriles IV ($R_2$ = CN) of Table II, and so the expedient was adopted of first methanolyzing them in the presence of HCl (*via* imino ether dihydrochlorides) to corresponding methyl esters, after which alkaline hydrolysis gave corresponding acids ($R_2$ = COOH), also listed in Table II. In cases where aminonitriles were not crystalline, this procedure served to identify them as the corresponding amino acids. The lack of reactivity of the functional group was indicated additionally by failure of lithium aluminum hydride reductions and Grignard reactions with the aminonitriles. The explanation for these effects can lie, not only in the polarizability of the amino group and the methine hydrogen α to cyano, either or both of which might permit charged-complex formation with polar reagents, but also in an electronic influence of the 4-amino group which, tending to place negative charge at ring positions 1, 3, and 5, opposes the normal distribution of charge over the phenylacetonitrile moiety and thus largely cancels out its reactivity.

**Biological Effects.**—Although compounds IVb–m of Table II did not appreciably affect adrenal cortical hormone output, the substances having specifically a 3-pyridyl group were active. Thus at doses ranging from 1–25 mg./kg., compound IVa ($R_2$ = CN) reduced the output of 11-hydroxy steroids, as determined (by Dr. H. Sheppard) through chromatographic analysis of dog adrenal vein steroids. Pharmacologically, IVa nitrile resembled amphenone B, causing delayed natriuresis in acute experiments and liver hypertrophy. Compound V caused a similar, marked decrease in 11-hydroxy steroid output, together with increased 11-desoxy steroid production. Thus, there

may be true similarity between the mode of action of these compounds and that shown by those of the amphenone and metyrapone series when tested by the same procedures,[7,10,37] although if this is the case it is rather surprising that nitriles IVb, IVd, and IVe ($R_2$ = CN) were not active. Acids listed in Table II, including IVa, b, and c ($R_2$ = COOH), were also inactive, and in several instances quite toxic. However, 1-(3-pyridyl)-2-(*p*-aminophenyl)ethane had a low order of activity similar to that of the more potent IVa (R = CN) and V.

## Experimental[38]

**Condensation of *p*-Nitrophenylacetonitrile with Aldehydes and Isatin.**—The following general procedure was used in all of these reactions to prepare compounds I. To a solution of 0.1 mole of aromatic carbonyl compound and 0.1 mole of *p*-nitrophenylacetonitrile in the minimum amount of warm methanol was added 10 ml. of piperidine. After an exothermic effect, if any, the deep purple solution was boiled on a steam cone for *ca.* 10 min., or until further thickening of the resulting suspension of crystals was not observed. After cooling, the product was collected and washed free of nearly all the purple mother liquor with methanol, then retriturated with the same solvent. Yields were determined after air drying the crystals, and samples for identification or analysis were prepared by further recrystallization from methanol. As observed in earlier work[15] with stilbenenitriles, even many repeated recrystallizations, resulting in no observable change in melting point or appearance, sometimes failed to give samples which yielded very accurate analytical figures. This difficulty was noticed particularly with oxyphenyl and basic derivatives. The *m*-hydroxybenzylidene compound (Ii) was highly solvated, giving even after vacuum drying, the following analysis.

*Anal.* Found: C, 56.52; H, 3.93; N, 8.35.

Principal ultraviolet maxima observed for several of the compounds (MeOH as solvent) indicated that, as in many previously known compounds of this type,[17] the isomers having the *trans*-stilbene geometry were at hand, since the most intense peak occurred at the longer wave length: Ic, $\lambda_{max}$ 252–259 and 309 mμ (ε 8040 and 20,550); If, $\lambda_{max}$ 261 and 446–450 mμ (ε 9940 and 27,710); Ih, $\lambda_{max}$ 262–266 and 315–318 mμ (ε 11,530 and 15,650); Ik, $\lambda_{max}$ 276 and 385 mμ (ε 6510 and 23,020); Il, $\lambda_{max}$ 278 and 374 mμ (ε 11,860 and 16,940); Im, $\lambda_{max}$ 280 and 364 mμ (ε 8790 and 19,320). However, the reverse was true in two cases, indicating *cis*-aryl groups about the double bond: Ia, $\lambda_{max}$ 219, 269, and 323–326 mμ (ε 12,760, 6350, and 2424); II, $\lambda_{max}$ 262, 336–341, and *ca.* 450 (ε 18,800, 13,400, and 1750). The infrared spectra (Nujol) of the nitronitriles uniformly had peaks in the 4.45–4.49-μ region.

**Condensation of *p*-Chlorophenylacetonitrile with Aldehydes.**—A solution of equivalent amounts of the two reactants in minimum warm methanol was treated with piperidine (10 ml./0.1 mole of nitrile) and boiled until the methanol had been removed. The residual oil was heated on the steam cone 1–2 hr. After cooling, the crystalline products III were purified using methanol. Ultraviolet spectra again indicated *trans*-stilbene structures: IIIa, $\lambda_{max}$ 230 and 313–316 mμ (ε 11,390 and 21,290); IIIb, $\lambda_{max}$ 230 and 307–309 mμ (ε 13,330 and 19,230). The infrared spectra (Nujol) showed peaks in the 4.45–4.50-μ region.

**Reduction of α-(*p*-Nitrophenyl)cinnamonitriles to α-(*p*-Aminophenyl)-β-arylpropionitriles. General Procedure.**—In a typical reduction, *ca.* 0.1 mole (in most cases, about 35 g.) of nitrostilbenenitrile, suspended or partly dissolved in *ca.* 350 ml. of ethyl acetate, was treated with 6–9 g. of commercial 10% palladium–charcoal catalyst, placed on a Parr hydrogenation apparatus, and shaken under 3.16–3.52 kg./cm.$^2$ initial hydrogen pressure. In a few cases the nitro compound was so sparingly soluble as to require gentle heating in the beginning to initiate reaction and gradual dissolution. In most cases the absorption of hydrogen began immediately and picked up speed, usually reaching a maximum rate of *ca.* 0.1406 kg./cm.$^2$ gauge pressure drop/min., as the exothermic reaction of nitro group(s) proceeded. When approximately 3 molar equiv. of hydrogen (per nitro group) had been absorbed, the rate of uptake slowed. At this point, with no interruption in shaking, the pressure on the reaction was restored to 3.16 kg./cm.$^2$ and external heating (70–80 v. on standard Parr heating element) was applied to maintain a temperature of *ca.* 75° for the remaining reaction time. Shaking was then continued, usually for about 0.5–1 hr. until the hydrogen absorption rate curve became nearly flat. It was found inadvisable in preliminary experiments to interrupt the uptake at any point prior to this, since doing so resulted in an incompletely reduced and usually air-unstable mixture of substances. The total amount of hydrogen taken up in each case, measured by gauge pressure drop after return to room temperature, is expressed in Table II as molar equivalents of $H_2$ per mole of compound reduced. These figures are empirical, and should not be regarded as accurate in any absolute sense, but rather only as a relative expression of the behavior of individual compounds in this series. The figures were calculated on the basis that a 0.5624 kg./cm.$^2$ gauge pressure drop represents uptake of 0.1 mole of $H_2$; this has been observed repeatedly with other compounds, but holds true only in the 3–4 atm. pressure range. Since some of the present compounds, notably dinitro ones, absorbed so much hydrogen initially as to nearly exhaust the 4-l. reserve tank, the relative molar expression in such cases is undoubtedly too high. However, in the interest of uniformity and simplicity in reporting these results, which seem to be fairly reproducible under the stated conditions, no attempt has been made to apply pressure *vs.* volume and other corrections needed to convert these empirically observed values to absolute ones.

After filtration to remove the catalyst, the solutions were evaporated. The aminonitriles, if crystalline, were isolated by trituration with ether, ethyl acetate, or mixtures of these solvents with cyclohexane. Further purification was effected by recrystallizing from the solvents indicated (Table II); prolonged drying *in vacuo* at *ca.* 60° was then often necessary to remove last traces of solvents before analysis, causing some difficulty in many instances in obtaining correct analytical figures. The aminonitriles uniformly showed infrared (Nujol) bands in the 4.42–4.45-μ region. No stable or well-characterized product could be isolated after reduction of the 2-pyridyl compound Ia. Crude aminonitriles which did not crystallize were esterified and hydrolyzed as described in the following experiment.

**Methanolysis and Hydrolysis of α-(*p*-Aminophenyl)-β-arylpropionitriles.**—In each case, 10 g. of aminonitrile was dissolved in 250 ml. of methanol; the solution was saturated with dry HCl, and refluxed 3–4 hr. Usually a precipitate (*p*-aminophenyl imino ether dihydrochloride) formed, necessitating care, or the addition of more methanol, because of bumping. After evaporation of most of the excess methanol, the cooled residue was treated with water and warmed about 5 min. on a steam cone to dissolve the hydrochloride. The aqueous solution was allowed to stand 1–3 days and was then treated with excess $Na_2CO_3$ in portions. The viscous product was extracted by vigorous shaking with ether and sufficient ethyl acetate to dissolve the gummy material. The separated organic solution, after washing with several portions of water, was dried ($K_2CO_3$), filtered, and evaporated. Virtually quantitative yields of crude amino esters, as viscous noncrystalline oils, were obtained.

The amino ester (*ca.* 10 g.) was treated first with about 20 ml. of methanol, then with 110 ml. of 10–11% NaOH solution, and the solution was refluxed 2–3 hr. The cooled solution was filtered clear and neutralized by addition of 20–22 ml. of concentrated HCl. The suspension was kept at 0° until no further precipitation of amino acid occurred; the product was collected, washed with two small portions of water, dried, and weighed (yield figures are given in Table II). For purification the amino acids were recrystallized from methanol, using Norit if necessary to decolorize.

Compound IVd formed a diaminonitrile dihydrochloride so sparingly soluble in methanol as to render the methanolysis procedure impractical.

Compound IVf nitrile also failed to methanolyze when subjected to the above procedure, giving what appeared to be the aminonitrile hydrochloride, m.p. *ca.* 200° dec., infrared 4.45 μ. Therefore direct hydrolysis with concentrated hydrochloric acid (10 g. was refluxed 4 hr. with 400 ml. of concentrated HCl) was employed in order to obtain the corresponding acid, which

(37) See G. deStevens, "Diuretics," Academic Press Inc., New York, N. Y., 1963, pp. 136–143, and additional references at end of Chapter VII.

(38) Melting points were determined using an air-bath apparatus with 360° thermometer, and are corrected by calibration against standard compounds.

was isolated as the **hydrochloride** (see Table II) directly from the cooled solution. The infrared spectra of the amino acids and hydrochlorides showed expected zwitterionic and carboxyl bands.

**1-(3-Pyridyl)-2-(*p*-nitrophenyl)ethylene.**—A warm solution of 16.3 g. (0.09 mole) of *p*-nitrophenylacetic acid and 11.2 g. (0.105 mole) of pyridine-3-aldehyde in 100 ml. of methanol was treated with 18 ml. of piperidine. When the exothermic reaction subsided, the brown solution was boiled for 2 hr., allowing most of the solvent to escape. Water (100 ml.) and concentrated HCl (16 ml.) were added to the cooled residue (effervescence). The gummy crystals, which appeared upon chilling the mixture, were washed with water and then warmed with 100 ml. of methanol. The cooled, crystalline suspension was filtered, and the product was washed with methanol. The yield of crude crystals, m.p. 129–136°, was 6.1 g. (25%). Purification by recrystallization from methanol gave bright yellow crystals, m.p. 152.5–155°.

*Anal.* Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.39. Found: C, 69.06; H, 4.50; N, 12.59.

**1-(3-Pyridyl)-2-(*p*-aminophenyl)ethane.**—Hydrogenation of 5.7 g. of nitro compound from the preceding experiment in the presence of 3.5 g. of 10% palladium–charcoal in ethyl acetate (160 ml.) and ethanol (160 ml.) under 2.81 kg./cm.$^2$ pressure resulted in exothermic uptake of 4.5 molar equiv. of hydrogen in 9 min. Filtration of the catalyst and evaporation of the solvents gave a crystalline product, the yield of which after ethyl acetate trituration was 2.2 g. (68%). Initially a solvated form, m.p. *ca.* 150–175° (sintering) was obtained; after recrystallization from aqueous methanol and drying *in vacuo*, the anhydrous form was secured as light grayish flakes, m.p. 117–119°.

*Anal.* Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.73; H, 6.97; N, 14.17.

**α-(*p*-Chlorophenyl)-β-(3-pyridyl)propionitrile (V).**—A solution of 11.7 g. of IIIa in 350 ml. of ethyl acetate was treated with 8 g. of 10% palladium–charcoal and shaken under 3.16 kg./cm.$^2$ of hydrogen, applying sufficient heat to gradually raise the temperature of the reaction to a maximum of 70°. The pressure began to drop slowly when the temperature reached *ca.* 50° and amounted to 0.28 kg./cm.$^2$ after 1 hr. At this point, the heating was discontinued, and the reaction was allowed to cool 1.5 hr. while continuing to shake; during this time excessive hydrogen (0.21 kg./cm.$^2$ pressure drop) was taken up. The filtered, greenish yellow solution was evaporated. From the remaining crude, discolored oil (air darkening) there was isolated, by means of trituration, first with ether–ethyl acetate and then with cyclohexane, a total of 1.8 g. (15%) of crude crystals, m.p. 76–80°. Recrystallization from cyclohexane raised the melting point to 86–88°. The infrared spectrum (Nujol) had a peak at 4.46 μ.

*Anal.* Calcd. for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; N, 11.54. Found: C, 69.52; H, 4.78; N, 11.71.

**α-(3,4-Dimethoxyphenyl)-β-phenylacrylonitrile.**—To a solution of 8.6 g. (0.374 g.-atom) of sodium in 700 ml. of methanol were added 65 g. (0.367 mole) of homoveratronitrile and 41 g. (0.387 mole) of benzaldehyde. The solution was boiled 1.5 hr., allowing about half of the solvent to escape. After cooling the suspension, the product was collected and washed with methanol; yield 89 g. (91%) of crystals, m.p. 85–87°, raised on further recrystallization from methanol to 86.5–88°; $\lambda_{max}^{Nujol}$ 4.49 μ; $\lambda_{max}^{EtOH}$ 236, 273, and 338 mμ (ε 13,300, 10,160, and 16,340), indicating *trans*-stilbene configuration.

*Anal.* Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.92; H, 5.82; N, 5.73.

**α-(3,4-Dimethoxyphenyl)-β-phenylpropionitrile.**—When a solution of 21.9 g. (0.0826 mole) of unsaturated nitrile from the preceding experiment in 300 ml. of ethyl acetate was shaken in the presence of 3 g. of 10% palladium–charcoal under 3.52 kg./cm.$^2$ of hydrogen, little or no uptake was noticed until the temperature of the mixture had been raised to about 50–60°. Then a slow pressure drop of 0.49–0.56 kg./cm.$^2$ took place in 0.5–0.7 hr. Absorption did not stop or even become appreciably slower at this point, and therefore the reaction was interrupted by discontinuing the application of heat and allowing to cool while shaking for about 1 hr., during which time an additional 0.07–0.14 kg./cm.$^2$ pressure drop occurred. The crude product, isolated by filtration and evaporation of the solution, crystallized after standing several days. Trituration with ether gave 19 g. (86%) of crystals, m.p. 73.5–77°. Recrystallization from ether raised the melting point to 76–78.5°, $\lambda_{max}^{Nujol}$ 4.46 μ.

*Anal.* Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.74; H, 6.57; N, 5.35.

The reaction mixture, immediately after hydrogenation, had a strong odor of amine or ammonia. From the oily material remaining after separation of the major product, as described above, no other crystalline products could be isolated. The amount of these by-products was increased, and the yield of above-described nitrile was correspondingly lowered, when the reduction was allowed to proceed past the point of *ca.* 1 molar equiv. of hydrogen uptake.

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