

Synthesis of Permethylnarciprimine and Permethylisonarciprimine

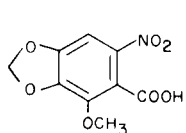
G. Savona and F. Piozzi

Institute of Organic Chemistry, University of Palermo, Palermo, Italy

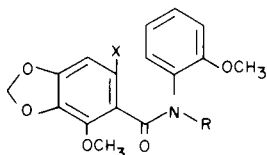
Received February 25, 1971

Recently we published preliminary communications on the syntheses of permethylnarciprimine (I) (1) and permethylisonarciprimine (II) (2). Now a full report on the experimental conditions is presented.

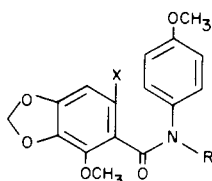
Starting material for the syntheses was 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (III), obtained as described by Wagner and Kuehl (3,4). Thionyl chloride treatment of III gave the acid chloride which was condensed with *N*-methyl-*o*-anisidine yielding the *N*-methylamide IV. The same product was more readily obtained by condensation of the acid chloride with *o*-anisidine followed by methyl sulfate *N*-methylation of the amide V. Catalytic hydrogenation afforded the aniline derivative VI, which was immediately diazotized without characterization.



III



IV R = CH₃ X = NO₂
 V R = H X = NO₂
 VI R = CH₃ X = NH₂

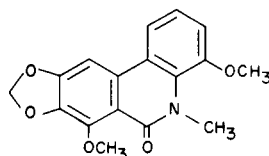


VII R = H X = NO₂
 VIII R = CH₃ X = NO₂
 IX R = CH₃ X = NH₂

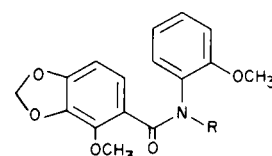
In the same manner, the acid chloride of III was condensed with *p*-anisidine, the amide VII was *N*-methylated to give VIII, and the latter was reduced to the aniline derivative IX which was also immediately diazotized without characterization.

The diazonium salt from VI was decomposed thermally, according to Hey (5,6) for the Pschorr synthesis of phen-

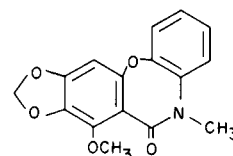
anthridones. Careful chromatography of the resulting mixture gave small amounts (2-3%) of permethylnarciprimine (I) and somewhat higher yields of the products X and XI, whose appearance had been foreseen based on previous papers (7,8).



I



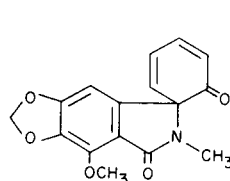
X R = H
 XII R = CH₃



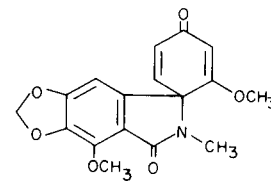
XI

Product X was identified on the basis of its mass spectra (M^+ = 301) and IR (3300 cm^{-1} , NH; 1650 cm^{-1} , amide CO). Product XI was assigned its structure on the basis of mass spectra (M^+ = 299) and IR (1640 cm^{-1} , amide CO; 1215 cm^{-1} , Ar-O-Ar).

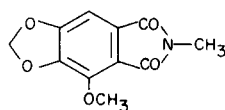
Precipitation as the fluoborate of the diazonium salt from VI and decomposition in the presence of copper gave a slightly better yield (4-5%) of permethylnarciprimine (I). This product was separated by chromatography from various by-products, *i.e.* X, XII, XIII and XIV, whose homologs had been found in similar cases by Hey (6,8,9).



XIII



XIV



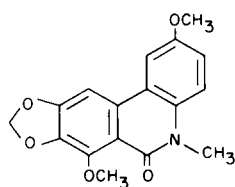
XV

Product XII was assigned its structure on the basis of mass spectra ($M^+ = 315$) and IR (1650 cm^{-1} , amide CO). The spirodienone XIII was identified by mass spectra ($M^+ = 299$) and IR (1665 cm^{-1} , cyclohexadienone CO; 1705 cm^{-1} , γ -lactam CO). The spirodienone structure XIV was elucidated after mass spectra ($M^+ = 329$) and IR (1655 cm^{-1} , cyclohexadienone CO; 1700 cm^{-1} , γ -lactam CO).

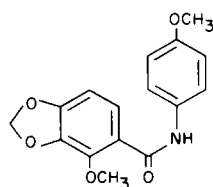
Another product, whose genesis seems rather unusual, was isolated in small quantity and was identified (m.p., IR, UV, NMR, MS) as cotarnic acid *N*-methylimide (XV). Minor products could not be isolated from the mixtures.

Synthetic permethylnarciprimine (I) was found (1) to be identical with the product of natural derivation.

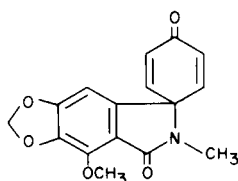
The diazonium salt from IX was precipitated as the fluoborate and decomposed in the presence of copper, giving a small yield (1%) of the expected permethylisonarciprimine (II), traces of the by-product XVI, and more consistent amounts of the spirodienone XVII (10-15%).



II



XVI



XVII

Product XVI was identified on the basis of mass spectra ($M^+ = 301$) and IR (3400 cm^{-1} , NH; 1655 cm^{-1} , amide CO); the spirodienone XVII was assigned its structure on the basis of mass spectra ($M^+ = 299$) and IR (1665 cm^{-1} , cyclohexadienone CO; 1698 cm^{-1} , γ -lactam CO). Minor products could not be isolated from the mixture.

Synthetic permethylisonarciprimine (II) was proved (2) to be identical with the product of natural derivation.

EXPERIMENTAL (10)

2-Methoxy-3,4-methylenedioxy-6-nitro-2'-methoxy-*N*-methylbenzanilide (IV).

(a)

A solution of 2-methoxy-3,4-methylenedioxy-6-nitrobenzoic acid (III) (3) (6 g.) in thionyl chloride (30 ml.) was refluxed for 2 hours and then excess thionyl chloride was evaporated under vacuum. The raw residue (uncharacterized) was added to a mixture of *N*-methyl-*o*-anisidine (11) (6.9 g.) and aqueous 10% potassium hydroxide (35 ml.) with vigorous stirring. After 10 minutes, the mixture was diluted with water and extracted with chloroform. Evaporation of this solvent gave a residue which was percolated through neutral alumina (eluent benzene-chloroform 7:3) and crystallized from ethanol to give IV, white powder m.p. $142\text{-}144^\circ$, yield 3.1 g.

Anal. Calcd. for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.47; N, 7.78. Found: C, 56.48; H, 4.42; N, 7.65.

(b)

Acid III (5 g.) was transformed into the chloride as described above. The raw product, dissolved in dry benzene (25 ml.), was added dropwise into an ice-cooled solution of *o*-anisidine (2.5 g.) in dry pyridine (20 ml.). After standing 24 hours at room temperature, the solution was poured into water and extracted with chloroform. Evaporation of the solvent gave 2-methoxy-3,4-methylenedioxy-6-nitro-2'-methoxybenzanilide (V), white powder m.p. $203\text{-}205^\circ$ (from acetone-ethanol), yield 6.5 g.

Anal. Calcd. for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.08; N, 8.09. Found: C, 55.62; H, 4.17; N, 7.93.

The product was dissolved in a mixture of acetone (150 ml.) and aqueous 10% sodium hydroxide (70 ml.). The boiling solution, to which methyl sulfate (5.2 ml.) had been added dropwise, was refluxed for 3 hours, diluted with water and extracted with chloroform. Evaporation of the solvent and crystallization from ethanol gave IV, m.p. $142\text{-}144^\circ$, yield 5.5 g.

2-Methoxy-3,4-methylenedioxy-6-nitro-4'-methoxybenzanilide (VII).

The acid chloride from 5 g. of acid III was condensed with *p*-anisidine (2.5 g.) under the identical conditions described for *o*-anisidine, yield of VII 6.4 g., white needles m.p. $193\text{-}195^\circ$ (from acetone-ethanol).

Anal. Calcd. for $C_{16}H_{14}N_2O_7$: C, 55.49; H, 4.08; N, 8.09. Found: C, 55.37; H, 4.02; N, 7.99.

2-Methoxy-3,4-methylenedioxy-6-nitro-4'-methoxy-*N*-methylbenzanilide (VIII).

N-Methylation of VII (6.3 g.) with methyl sulfate, as described for V, gave VIII, white powder m.p. 142° (from ethanol), yield 5.4 g.

Anal. Calcd. for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.47; N, 7.78. Found: C, 56.80; H, 4.59; N, 7.62.

Reduction of IV, Diazotization and Thermal Decomposition of the Diazonium Salt.

A solution of IV (1.5 g.) in ethanol (60 ml.) was hydrogenated on 10% Pd-C at room temperature and atmospheric pressure, then filtered and evaporated. The oily residue (VI) was dissolved in warm 0.7 *N* sulfuric acid and diazotized at 0° with sodium nitrite (0.6 g.). After 1 hour stirring at 0° , the temperature was raised to and kept at 70° until nitrogen evolution ceased. The solution was extracted with chloroform and the extract was

washed with 10% sodium hydroxide, dried and evaporated. The residue was dissolved in benzene and chromatographed on silica gel (40 g.), eluting with benzene-ethyl acetate mixtures of increasing content of ethyl acetate. Rechromatography of the enriched fractions gave products X, I and XI.

2-Methoxy-3,4-methylenedioxy-2'-methoxybenzamide (X).

This compound crystallizes from methanol as white scales, m.p. 150°, yield 100 mg.; MS: 301 m/e (M^+); IR: 3300 cm^{-1} (NH), 1650 cm^{-1} (amide CO).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.86; H, 5.11; N, 4.54.

4,7-Dimethoxy-8,9-methylenedioxy-5-methylphenanthridone (I) (Permethylnarciprimine).

This compound crystallized from methanol giving colorless prisms, m.p. 198°, no depression at m.m.p. with permethylnarciprimine of natural derivation (1). MS, IR UV and NMR data were already reported (1).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.01; H, 4.66; N, 4.39.

The lactam of 2-methoxy-3,4-methylenedioxy-6-(*o*-methylaminophenoxy)benzoic acid (XI) gave white needles, m.p. 175° (from methanol), yield 100 mg.; MS: 299 m/e (M^+); IR: 1640 cm^{-1} (amide CO), 1215 cm^{-1} (Ar-O-Ar); NMR (deuteriochloroform): 3.57 δ (s, NCH_3), 4.04 δ (s, OCH_3), 5.91 δ (s, $O-CH_2-O$), 6.43 δ (s, 1 Ar-H), 7.14 δ (apparent s, 4 Ar-H).

Reduction of IV, Diazotization and Decomposition of the Diazonium Fluoborate.

The oily product from catalytic hydrogenation of IV (5.4 g.) was dissolved in 4 *N* hydrochloric acid (60 ml.) and diazotized with sodium nitrite (1.5 g.). After 1 hour stirring, dropwise addition of a sodium fluoborate (5 g.) solution in water (15 ml.) gave a precipitate of diazonium fluoborate which was collected, washed with ice-cold water followed by ether, and dried. To a solution of the fluoborate in acetone (200 ml.) was added copper powder (4 g.) and stirring was continued until nitrogen evolution ceased. After filtration, the solution was poured into water and extracted with chloroform. Treatment as described above and chromatography gave in order compounds X (100 mg.), XV (20 mg.), XII (100 mg.), I (200-250 mg.), XIII (150-200 mg.) and XIV (100-150 mg.).

2-Methoxy-3,4-methylenedioxy-2'-methoxybenzamide (X).

This compound was identified as described above.

Cotarnic Acid *N*-Methylimide (XV).

This compound was a yellowish powder, m.p. 205° (from methanol) and was identified (m.m.p., IR, UV, NMR, MS) by comparison with a sure specimen: NMR (deuteriochloroform): 3.11 δ (s, NCH_3), 4.21 δ (s, OCH_3), 6.11 δ (s, $O-CH_2-O$), 6.95 δ (s, 1 Ar-H).

2-Methoxy-3,4-methylenedioxy-2'-methoxy-*N*-methylbenzamide (XII).

This compound gave large white prisms, m.p. 165° (from methanol); MS: 315 m/e (M^+); IR: 1650 cm^{-1} (amide CO); NMR (deuteriochloroform): 3.28 δ (s, NCH_3), 3.75 and 3.88 δ (s, 2 OCH_3), 5.70 δ (s, $O-CH_2-O$), 6.10-7.20 δ (complex pattern, 6 Ar-H).

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.59; H, 5.36; N, 4.28.

Permethylnarciprimine (I).

This compound was identified as described above.

The spirodienone XIII crystallized as yellow prisms, m.p. 200-202° (from methanol or acetone); MS: 299 m/e (M^+); IR: 1665 cm^{-1} (cyclohexadienone CO), 1705 cm^{-1} (γ -lactam CO); NMR (deuteriochloroform): 2.75 δ (s, NCH_3), 4.05 δ (s, OCH_3), 5.85 δ (s, $O-CH_2-O$), 6.26 δ (s, 1 Ar-H), 5.90-7.30 δ (complex pattern, 4 Ar-H).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.45; H, 4.34; N, 4.63.

The spirodienone XIV gave pale yellow plates, m.p. 230° (from methanol); MS: 329 m/e (M^+); IR: 1655 cm^{-1} (cyclohexadienone CO), 1700 cm^{-1} (γ -lactam CO); NMR (deuteriochloroform): 2.78 δ (s, NCH_3), 3.59 and 4.15 δ (s, 2 OCH_3), 5.95 δ (s, $O-CH_2-O$), 5.72 δ (d, $J_{meta} = 1.2$ Hz, 1 Ar-H), 6.22 δ (s, 1 Ar-H), 6.17 δ (d, $J_{ortho} = 9.5$ Hz, 1 Ar-H), 6.32 δ (dd, $J_{meta} = 1.2$ Hz, $J_{ortho} = 9.5$ Hz, 1 Ar-H).

Anal. Calcd. for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.87; H, 4.47; N, 4.14.

Reduction of VIII, Diazotization and Decomposition of the Diazonium Fluoborate.

The nitro derivative VIII was reduced catalytically as described for IV. The oily product from 5.4 g. of VIII was diazotized and transformed into the diazonium fluoborate which was dissolved in acetone (200 ml.) and stirred with copper powder until nitrogen evolution ceased. The mixture was filtered, diluted with water and extracted with chloroform. Evaporation of the solvent gave a residue which was dissolved in benzene and 5% chloroform, then eluted on silica gel with benzene-ethyl acetate mixtures of increasing content of ethyl acetate. In order were isolated products XVI (20 mg.) and XVII (600-700 mg.); rechromatography of the mother liquor from crystallization of XVII gave a small amount (30 mg.) of II.

2-Methoxy-3,4-methylenedioxy-4'-methoxybenzamide (XVI).

This compound crystallized from methanol as a white powder, m.p. 136-138°; MS: 301 m/e (M^+); IR: 3400 cm^{-1} (NH), 1655 cm^{-1} (amide CO).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.62; H, 4.86; N, 4.50.

The spirodienone XVII gave pale yellow scales, m.p. 275° (from methanol); MS: 299 m/e (M^+); IR: 1665 cm^{-1} (cyclohexadienone CO), 1698 cm^{-1} (γ -lactam CO); NMR (deuteriochloroform): 2.90 δ (s, NCH_3), 4.15 δ (s, OCH_3), 5.98 δ (s, $O-CH_2-O$), 6.30 δ (s, 1 Ar-H), 6.40 δ (s, 4 Ar-H).

Anal. Calcd. for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.30; H, 4.48; N, 4.55.

2,7-Dimethoxy-8,9-methylenedioxy-5-methylphenanthridone (II) (Permethylnarciprimine).

This compound gave white needles, m.p. 175-176° (from methanol), no depression at m.m.p. with permethylnarciprimine of natural derivation (2,12); IR, UV and NMR data were identical with those already reported (12).

Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.34; H, 4.78; N, 4.32.

This work was supported by C.N.R. (National Research Council), Roma, Italy.

REFERENCES

- (1) G. Savona, F. Piozzi and M. L. Marino, *Chem. Commun.*, 1006 (1970).
- (2) G. Savona and F. Piozzi, *Chem. Ind. (London)*, 1627 (1970).
- (3) A. F. Wagner and F. A. Kuehl, U. S. Patent 3,000,902; *Chem. Abstr.*, 56, 1399 (1962).
- (4) For the improved preparation of some intermediates, see F. Dallacker, *Chem. Ber.*, 102, 2663 (1969).
- (5) R. A. Heacock and D. H. Hey, *J. Chem. Soc.*, 1508 (1952).
- (6) D. H. Hey, J. A. Leonard, T. M. Moynahan and C. W. Rees, *ibid.*, 232 (1961).
- (7) D. H. Hey and D. G. Turpin, *ibid.*, 2471 (1954).
- (8) D. H. Hey, J. A. Leonard, C. W. Rees and A. R. Todd, *ibid. (C)*, 1513 (1967).
- (9) D. H. Hey, C. W. Rees and A. R. Todd, *ibid. (C)*, 1518 (1967).
- (10) All melting points were taken in capillary tubes and are uncorrected. IR (nujol) and UV (ethanol) spectra were registered on Perkin Elmer Infracord 137 and Beckman DB spectrometers, respectively. Mass spectra were recorded on a Hitachi Perkin Elmer RMU-6D instrument (70 eV, direct inlet system) at the Institute of Chemistry, Politechnic School of Milano, by the courtesy of Dr. A. Selva. NMR spectra were registered at 60 MHz on a C-60 H Jeol instrument, using TMS as internal standard. Column chromatographies were carried on neutral or basic Merck alumina, or on Merck silica gel; fractions were monitored by TLC on Merck silica gel G.
- (11) Prepared by a variant of the general method proposed by E. Thielepape, *Ber.*, 68, 751 (1935). *N*-Acetyl-*o*-anisidine was treated with sodium hydride and then with methyl sulfate to give *N*-methyl-*N*-acetyl-*o*-anisidine. The latter underwent acid hydrolysis to the required product, whose purity was checked by GLC.
- (12) F. Piozzi, C. Fuganti, R. Mondelli and G. Ceriotti, *Tetrahedron*, 24, 1119 (1968).