by linear regression from the experimental data with $a = 0.165$ and $b = 0.105$. The latter values are obtained by injecting standard solutions of I and II and measuring the ratios of *m/e* 182 to 181 and of *m/e* 181 to 182, respectively. The equation is given by:

$$y = 0.05x + 0.0013 \qquad \text{(Eq. 5)}$$

where y is the corrected areas ratio and x is the mescaline concentration.

Curve 2 is calculated with $a = 0$ and $b = 0.105$ when no corrections are made for the constant contribution of the internal standard's *m/e* 181 ion to the compound to be measured. In this case, the intercept is 0.17, which is in reasonably good agreement with the expected value of 0.165.

An example of a mass fragmentogram of a plasma extract is shown in Fig. 3. No coeluting substances were found when blank plasma samples were analyzed. Therefore, the method, due to the combined specificity of both retention time and mass spectrometric fragmentation pattern, is suitable for pharmacokinetic studies.

The influence of the overnight storage temperature was examined by analyzing a 0.05-ppm spiked pool serum sample, part of which had been kept at 4° and another part at −18° overnight (Table I). The mean values ($n = 6$) of each set of assays were not significantly different (Student *t* test).

The precision of this analytical procedure, expressed as the coefficient of variation, is on the order of 5%. For the GLC–mass spectral quantitative assay, it was 1.7% (six repetitive injections of the same extract).

Although the apparent extraction efficiency with a labeled internal standard added before the extraction was 100%, the actual efficiency was checked; it was about 95% for spiked serum samples. To illustrate that the method is suitable for biological profile studies, the profile curve of one subject is shown in Fig. 4.

REFERENCES

(1) G. J. Kapadia and M. B. E. Fayez, *J. Pharm. Sci.*, **59,** 1699 (1970).

(2) I. Cohen and W. H. Vogel, *Experientia*, **26,** 1231 (1971).

(3) J. Cochin and J. W. Daly, *ibid.*, **18,** 294 (1962).

(4) M. P. Kullberg and C. W. Gorodetzky, *Clin. Chem.*, **20,** 177 (1974).

(5) R. J. Bussey and R. C. Backer, *ibid.*, **20,** 302 (1974).

(6) J. A. Vinson, J. E. Hooyman, and C. E. Ward, *J. Forensic Sci.*, **20,** 552 (1975).

(7) A. N. Masoud, *J. Pharm. Sci.*, **65,** 1585 (1976).

(8) A. C. Moffat, A. H. Stead, and K. W. Smalldon, *J. Chromatogr.*, **90,** 19 (1974).

(9) A. Wu, *Clin. Toxicol.*, **8,** 225 (1975).

(10) R. C. Gupta and G. D. Lundberg, *ibid.*, **11,** 437 (1977).

(11) M. L. Chan, C. Whetsell, and J. D. McChesney, *J. Chromatogr. Sci.*, **12,** 512 (1974).

(12) L. J. Riceberg, H. Van Vunakis, and L. Levine, *Anal. Biochem.*, **60,** 551 (1974).

(13) K. D. Charalampous, K. E. Walker, and J. Kinross-Wright, *Psychopharmacologia*, **9,** 48 (1966).

New Compounds: Reissert Compound Studies XXXII: Facile Synthesis of 3-Azapapaverine

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Abstract □ 6,7-Dimethoxyphthalazine was obtained in four steps from veratric acid and converted to its Reissert compound. Alkylation of this Reissert compound with 3,4-dimethoxybenzyl chloride followed by hydrolysis gave 3-azapapaverine.

Keyphrases □ Reissert compounds—synthesis of 3-azapapaverine from veratric acid □ 3-Azapapaverine—synthesis from veratric acid *via* a Reissert compound □ Phthalazines—synthesis of 3-azapapaverine from veratric acid *via* Reissert compound derivative of 6,7-dimethoxyphthalazine

The application of Reissert compounds (1, 2) to the synthesis of natural products and compounds of potential medicinal interest is well documented (2, 3) in the field of quinolines and, particularly, isoquinolines. Although phthalazine also yields a Reissert compound (4, 5), its use in the synthesis of potential medicinal agents has not been studied. This paper reports a convenient synthesis of 3-azapapaverine (I) using the Reissert compound (II) of 6,7-dimethoxyphthalazine (III) and demonstrates the potential utility of Reissert compounds derived from phthalazine.

DISCUSSION

A convenient synthesis of III from commercially available veratric acid (IV) was developed using modifications of several literature procedures. Chloromethylation of IV gave the lactone (V) (6), which yielded 4,5-dimethoxyphthalyl alcohol (VI) on reduction with lithium aluminum hydride (7). Oxidation of VI with activated manganese dioxide gave 4,5-dimethoxyphthalaldehyde (VII). Treatment of this dialdehyde (VII) with hydrazine hydrate gave III (8). The overall yield of III from IV was 36%.

Compound III was converted to its Reissert compound (II) by a phase transfer procedure (5) or by a trimethylsilyl cyanide procedure (9). Alkylation of II with 3,4-dimethoxybenzyl chloride in the presence of sodium hydride gave the alkylated Reissert compound VIII. Hydrolysis of VIII with potassium hydroxide gave I.

This procedure should be valuable in the synthesis of phthalazine analogs of isoquinolines of medicinal interest.

EXPERIMENTAL

***m*-Meconin (V)**—Formaldehyde (230 ml, 37% solution) was saturated with hydrogen chloride gas at 15–20°, and 32 g (0.176 mole) of IV[1] was added. The mixture was heated to 60–70° for 7 hr, during which hydrogen chloride gas was bubbled slowly through it. The mixture was cooled, kept overnight, and concentrated *in vacuo*. Water, 100 ml, was added, and the mixture was neutralized with 2:3 dilute ammonium hydroxide. A solid formed and was filtered, washed several times with water, and dried. Recrystallization from methanol gave 22.4 g (65.6%) of V, mp 154–155° [lit. (6) mp 154–156°]; IR (KBr): 3080, 3020 (m), 2940 (w), 1755–1740 (s), 1600 (s), 1500 (s), 1350 (s), and 1300 (s) cm^{-1}.

4,5-Dimethoxyphthalyl Alcohol (VI)—A warm solution of 14 g (0.072 mole) of V in 150 ml of anhydrous tetrahydrofuran was added continuously to a suspension of 7.5 g of lithium aluminum hydride in 80 ml of tetrahydrofuran, and the mixture was refluxed for 4 hr. The mixture was cooled in an ice bath, and the excess lithium aluminum hydride was

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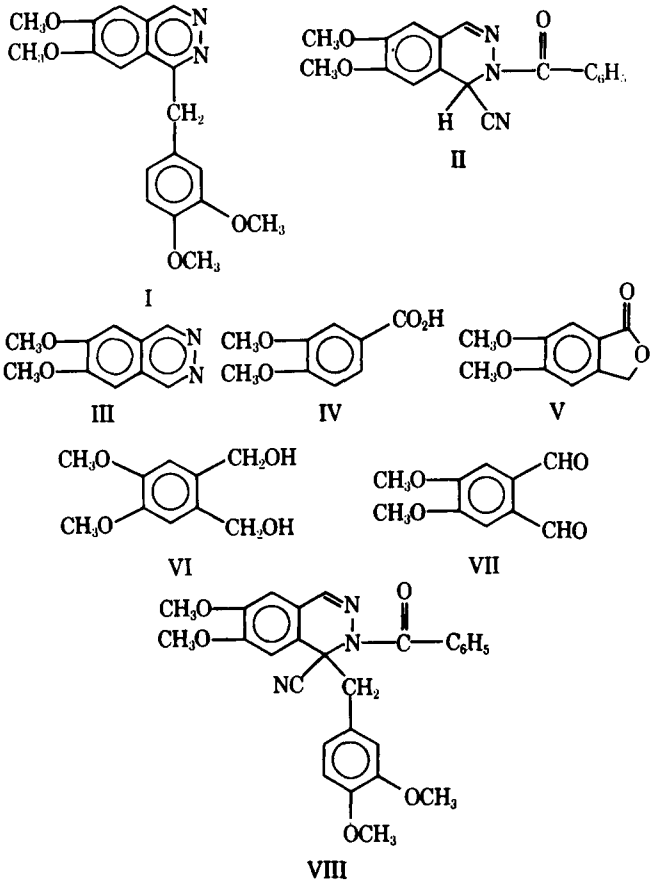

decomposed by the dropwise addition, with stirring, of 7.5 ml of water, 7.5 ml of 15% NaOH, and 22.5 ml of water. The precipitate was extracted with hot tetrahydrofuran, the combined tetrahydrofuran solutions were evaporated, and the residue was extracted with chloroform. Evaporation of the dried chloroform extract gave 13 g (91%) of VI, mp 110–111° (from benzene) [lit. (7) mp 111°].

4,5-Dimethoxyphthalaldehyde (VII)—To a vigorously stirred suspension of 20 g of activated manganese dioxide in 200 ml of chloroform was added 3 g of VI, and the mixture was stirred at room temperature for 3 days. The manganese dioxide was filtered and washed several times with chloroform, and the combined solvent was distilled to give 1.9 g (64.6%) of VII, mp 168–169° (from benzene) [lit. (7) mp 165°]; IR (KBr): 3100, 3000, 2930, 2870 (w), 1675 (vs), 1585 (s), 1510–1500 (s), 1460 (s), 1440 (s), and 1285 (s) cm^{-1}; NMR ($CDCl_3$): δ 10.7 (s, 2H), 7.36 (s, 2H), and 3.98 (s, 6H).

6,7-Dimethoxyphthalazine (III)—Compound VII (3.5 g, 0.018 mole) was warmed with 175 ml of absolute ethanol, and 1.1 g of 85% hydrazine hydrate was added dropwise with stirring. When VII had dissolved, the solution was refluxed for 5 hr and concentrated *in vacuo* to give 3.2 g (93.4%) of III, mp 198–200° (from chloroform–benzene) [lit. (8) mp 181–183°]; IR ($CHCl_3$): 3050 (m), 1605 (w), 1505 (m), 1470 (m), 1430 (s), 1335 (m), 1250 (s), 1225 (vs), and 1160 (s) cm^{-1}; NMR ($CDCl_3$): δ 9.27 (s, 2H), 7.1 (s, 2H), and 4.04 (s, 6H).

Anal.—Calc. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30. Found: C, 63.41; H, 5.53.

1-Cyano-2-benzoyl-6,7-dimethoxy-1,2-dihydrophthalazine (II)—To a solution of 3.2 g (0.0168 mole) of III in 200 ml of dry methylene chloride were added a catalytic amount (50 mg) of anhydrous aluminum chloride and 5 g (0.0504 mole) of trimethylsilyl cyanide. After 10 min, 7.1 g (0.0504 mole) of benzoyl chloride was added, and the mixture was stirred at room temperature for 24 hr. The mixture was washed with water, 5% HCl, water, 5% NaOH, and water. The mixture was dried, and the solvent was removed. The residue was recrystallized from benzene–chloroform to give 5 g (92.6%) of II, mp 204–207°; IR (KBr): 3080 (w), 2975 (m), 2945 (w), 1640 (s), 1600 (s), 1570 (w), 1515 (s), 1450 (s), 1380 (s), 1315 (s), 1280 (s), 1250 (s), 1130 (s), 1010 (s), and 910 (s) cm^{-1}; NMR ($CDCl_3$): δ 7.78–7.20 (m, 6H), 6.86 (s, 1H), 6.82 (s, 1H), 6.55 (1H), 3.95 (s, 3H), and 3.92 (s, 3H).

Anal.—Calc. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.28; H, 4.63; N, 13.02.

1-Cyano-1-(3,4-dimethoxybenzyl) -2- benzoyl-6,7-dimethoxy-1,2-dihydrophthalazine (VIII)—To a stirred solution of 3.21 g (0.01 mole) of II in 30 ml of dimethylformamide at −15° under a nitrogen atmosphere were added 1.87 g (0.01 mole) of 3,4-dimethoxybenzyl chloride and 0.48 g of 50% NaH in oil. The mixture was allowed to warm to room temperature and was stirred for an additional 2 hr. Then the solution was poured onto 300 g of ice. The product was filtered, washed with water, and dried to give 4.48 g (95%) of VIII, mp 198–201° (from chloroform–methanol); IR (KBr): 3070 (w), 3045 (w), 3010 (m), 2945 (w), 2850 (m), 1655 (s), 1600 (s), 1570 (m), 1510 (s), 1410 (s), 1330 (s), 1260 (s), 1240 (s), and 1120 (s) cm^{-1}; NMR ($CDCl_3$): δ 7.78–6.20 (m, 11H), 3.9 (s, 3H), 3.8 (s, 6H), 3.65 (s, 3H), and 3.56 (s, 2H).

Anal.—Calc. for $C_{27}H_{25}N_3O_5$: C, 68.78; H, 5.34; N, 8.91. Found: C, 68.85; H, 5.24; N, 8.88.

3-Azapapaverine (I)—A solution of 4.4 g of VIII and 47 g of potassium hydroxide in 140 ml of ethanol and 140 ml of water was refluxed for 3 hr. The mixture was concentrated *in vacuo* to less than half the volume, and 140 ml of water was added. The mixture was extracted with chloroform, and the dried chloroform extract was evaporated to give I (74% yield), mp 120° (from ethyl acetate–petroleum ether) [lit. (10) mp 120–121°].

Treatment of I in methanol with methyl iodide gave I methiodide, mp 203–208° (from ethanol); IR (KBr): 3010 (m), 2965 (m), 2920 (w), 2850 (m), 1595 (s), 1510 (vs), 1415 (s), 1300 (s), 1220 (s), 1150 (s), and 1030 (s) cm^{-1}; NMR (acetone-d_6): δ 10.35 (s, 1H), 7.98 (s, 1H), 7.9 (s, 1H), 7.05 (s, 1H), 6.83 (broad s, 2H), 4.73 (s, 2H), 4.68 (s, 3H), 4.11 (s, 3H), 4.08 (s, 3H), and 3.71 (s, 6H).

Anal.—Calc. for $C_{20}H_{23}IN_2O_4$: C, 49.80; H, 4.80; N, 5.80. Found: C, 49.77; H, 4.81; N, 5.89.

REFERENCES

(1) F. D. Popp, *Adv. Heterocycl. Chem.*, **9**, 1 (1968).

(2) *Ibid.*, **24**, 187 (1979).

(3) F. D. Popp, *Heterocycles*, **1**, 165 (1973).

(4) F. D. Popp, J. M. Wefer, and C. W. Klinowski, *J. Heterocycl. Chem.*, **5**, 879 (1968).

(5) D. Bhattacharjee and F. D. Popp, *Heterocycles*, **6**, 1905 (1977).

(6) T. Ikeda, S. Kanahara, and T. Ujiie, *Kanazawa Daigaku Yakugukubu, Kenkya Nempo*, **8**, 1 (1958).

(7) J. Blair, W. R. Logan, and G. T. Newbold, *J. Chem. Soc.*, **1956**, 2443.

(8) A. V. El'tsov and A. A. Ginesina, *Zh. Org. Khim.*, **3**, 191 (1967).

(9) S. Ruchirawat, N. Phadungkul, M. Chaunkamnerdkarn, and C. Thebtaranonth, *Heterocycles*, **6**, 43 (1977).

(10) T. Ikeda and S. Kanahara, *Kanazawa Daigaku Yakugukubu, Kenkya Nempo*, **10**, 15 (1960).