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36. *Colchicine and Related Compounds. Part II. Synthesis of a Simple Analogue of* N-*Acetylcolchinol Methyl Ether.*

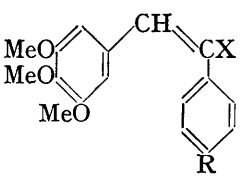
By J. W. Cook and Lewis L. Engel.

As a preliminary to a synthetic approach to the colchicine structure condensations have been carried out between 3 : 4 : 5-trimethoxybenzaldehyde and phenylacetonitrile, phenylacetic acid, and their *p*-methoxy-derivatives. From one of the condensation products was obtained a compound (III) which may have a structural relationship to a colchicine degradation product. Biological examination suggested that further attention should be given to this type of compound.

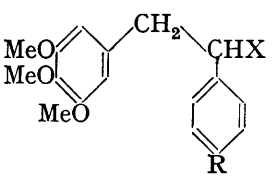
Application of Pschorr's method to the synthesis of phenanthrene derivatives having structures similar to that proposed by Windaus for colchicine (see preceding paper) is limited by the poor yield of 2-nitro-compound formed by the nitration of 3 : 4 : 5-trimethoxybenzaldehyde (Sharp, J., 1936, 1234). The experiments now recorded were carried out in 1937 with the dual object of preparing for biological test dicyclic compounds having a structural resemblance to derivatives of colchicine, and of studying, in these dicyclic compounds, reactions which might be applied subsequently to the less accessible phenanthrene derivatives. The closest approach to the colchicine type of structure was realised with a derivative of diphenylpropylamine (III), which, if cyclised by elimination of two hydrogen atoms, would give a structure which has been under consideration for *N*-acetylcolchinol methyl ether (compare Part I).

The effect of (III) on mitosis in the liver of the rat was examined by Dr. A. M. Brues of Harvard Medical School, who reported that "10 mg. gave a completely abnormal nuclear picture, and 1 mg. gave a slightly modified picture. Probably owing to the low solubility of this compound, these effects were hardly visible after one day and were at their best four days after a single dose. The fatal dose of this compound was 100 mg., and death occurred in opisthotonic convulsions as in the case of poisoning with strychnine and a number of other alkaloids." Thus it seems that this synthetic compound has something of the biological properties of alkaloids containing condensed ring systems, and the examination of a series of related compounds is being undertaken. It has long been known in the case of nicotine and cocaine that the complete ring systems of these alkaloids are not essential for their biological effects, and it has recently been shown (Buth, Külz, and Rosenmund, *Ber.*, 1939, **72**, 19) that a whole series of dicyclic compounds, mostly bis(phenylethyl)amine derivatives, have the spasmolytic action of papaverine and its tetrahydride.

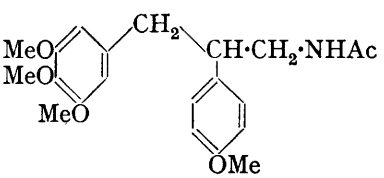
Condensation of sodium phenylacetate with 3 : 4 : 5-trimethoxybenzaldehyde by the Perkin method led to *α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)acrylic acid* (I; R = H, X = CO_2H). By hydrogenation over palladium-black this was smoothly converted into *α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)propionic acid* (II; R = H, X = CO_2H), which was



(I.)



(II.)



(III.)

also obtained by hydrolysis of a reduction product of *α-cyano-α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)ethylene* (I; R = H, X = CN). This cyano-compound was formed in good yield by condensation of phenylacetonitrile and 3 : 4 : 5-trimethoxybenzaldehyde by means of dilute alkali solution. It was hoped that the saturated acid (II; R = H, X = CO_2H) could be nitrated in the methoxylated ring to give a nitro-acid which could be used in the Pschorr phenanthrene synthesis. However, nitration experiments led to profound decomposition of the acid.

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Condensation was also effected between sodium *p*-anisylacetate and 3 : 4 : 5-trimethoxybenzaldehyde. In addition to the expected α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)-*acrylic acid* (I; R = OMe, X = CO_2H), there was also isolated 3 : 4 : 5 : 4′-*tetramethoxystilbene* (I; R = OMe, X = H) and a second neutral product which gave values for carbon and hydrogen pointing to the *anhydride* of the acid (I; R = OMe, X = CO_2H). α-*Cyano*-α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; R = OMe, X = CN) was obtained in 85% yield from *p*-methoxyphenylacetonitrile and 3 : 4 : 5-trimethoxybenzaldehyde. Catalytic hydrogenation with platinum oxide effected reduction of the nitrile to β-p-*anisyl*-γ-(3 : 4 : 5-*trimethoxyphenyl*)*propylamine* (II; R = OMe, X = $CH_2{\cdot}NH_2$), which gave an N-*acetyl* derivative (III), possibly closely related in structure to the tricyclic *N*-acetylcolchinol methyl ether. A by-product in the hydrogenation was the saturated nitrile (II; R = OMe, X = CN), which gave on hydrolysis the corresponding *acid*, identical with that obtained from *p*-anisylacetic acid.

Experimental.

(All m.p.'s are corrected.)

3 : 4 : 5-Trimethoxybenzaldehyde was prepared as described by Nierenstein (*J. pr. Chem.*, **1931**, **132**, 200) (compare Slotta and Heller, *Ber.*, 1930, **63**, 3042). Its *anil*, obtained by 1 hour's heating at 100° of molecular proportions of the aldehyde and aniline, formed colourless rhombs, m. p. 89—90° (from aqueous methyl alcohol) (Found: C, 70·6; H, 6·4. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3%). The yield of 2-nitro-3 : 4 : 5-trimethoxybenzaldehyde obtained from the nitration products of this anil was no more satisfactory than from direct nitration of the aldehyde (Sharp, *loc. cit.*).

α-*Phenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*acrylic Acid* (I; R = H, X = CO_2H).—A mixture of sodium phenylacetate (9 g.), 3 : 4 : 5-trimethoxybenzaldehyde (9·8 g.), and acetic anhydride (25 c.c.) was heated at 150—160° for 5 hours, cooled, poured on ice, and kept overnight. The pasty mass was collected and extracted with warm dilute sodium carbonate solution, and the alkaline solution shaken with ether and then acidified. The precipitated α-*phenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*acrylic acid* was crystallised from aqueous alcohol and then benzene–*cyclo*hexane and formed fine silky needles (5·5 g.), m. p. 186—187° (Found: C, 68·9; H, 5·8. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·8%). The p-*phenylphenacyl* ester formed microscopic prismatic needles, m. p. 123·5—124·5° (Found: C, 75·55; H, 5·5. $C_{32}H_{28}O_6$ requires C, 75·6; H, 5·55%). Hydrogenation of the acrylic acid (4·8 g.) in acetic acid (75 c.c.) with palladium-black (0·4 g.) was complete in 4 hours at room temperature. The liquid α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)propionic acid (II; R = H, X = CO_2H) so formed (3·9 g.; b. p. 215—219°/0·5 mm.) gave a p-*phenylphenacyl* ester as a colourless microcrystalline powder, m. p. 94—95° (Found: C, 75·1; H, 5·9. $C_{32}H_{30}O_6$ requires C, 75·3; H, 5·9%).

α-*Cyano*-α-*phenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; R = H, X = CN).—Condensation of phenylacetonitrile (4·1 g.) with 3 : 4 : 5-trimethoxybenzaldehyde (6·9 g.) in alcoholic solution (25 c.c.) was effected by vigorous shaking after addition of aqueous sodium hydroxide (1·4 g. in 3 c.c.). The solution was acidified and the precipitate was collected and recrystallised, once from aqueous alcohol and twice from methyl alcohol. α-*Cyano*-α-*phenyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (6·8 g.) formed small colourless prisms, m. p. 77—79° (Found: C, 74·1; H, 5·9. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8%). When this nitrile was shaken with hydrogen and a platinum oxide catalyst in alcoholic solution at 60°, the absorption of hydrogen corresponded with only one molecule. The product was hydrolysed by 11 hours' boiling with 25% alcoholic potash and gave an oily acid, which was identified through its *p*-phenylphenacyl ester, m. p. 95°, as α-phenyl-β-(3 : 4 : 5-trimethoxyphenyl)propionic acid.

α-p-*Anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*acrylic Acid* (I; R = OMe, X = CO_2H).—*p*-Anisylacetonitrile and *p*-anisylacetic acid were obtained from anisaldehyde as described by Kindler and Peschke (*Arch. Pharm.*, 1933, **271**, 431). A mixture of 3 : 4 : 5-trimethoxybenzaldehyde (9·8 g.), sodium *p*-anisylacetate (9·4 g.), and acetic anhydride (25 c.c.) was heated for 5 hours in an oil-bath at 140—160°. The mixture was cooled, poured on ice, and kept overnight. The acidic product was extracted with warm sodium carbonate solution and gave, after recrystallisation from benzene and then toluene, almost colourless elongated plates (4·9 g.) of α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*acrylic acid*, m. p. 207—208° (Found: C, 66·5; H, 6·0. $C_{19}H_{20}O_6$ requires C, 66·2; H, 5·9%). The *ethyl* ester, prepared through the silver salt, formed colourless leaflets, m. p. 84—85° (Found: C, 67·6; H, 6·6. $C_{21}H_{24}O_6$ requires C,

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67·7; H, 6·5%), and the p-*phenylphenacyl* ester formed colourless elongated plates, m. p. 169—170° (Found: C, 73·2; H, 5·7. $C_{33}H_{30}O_7$ requires C, 73·6; H, 5·6%).

The neutral products from the above condensation were recrystallised from acetone–light petroleum and could then be separated mechanically into two components. One of these, present in small amount, crystallised from acetone–light petroleum in large yellowish prisms, m. p. 159·5—160·5°, and consisted of 3 : 4 : 5 : 4′-*tetramethoxystilbene* (Found: C, 72·0; H, 6·75. $C_{18}H_{20}O_4$ requires C, 71·95; H, 6·7%). The major neutral product appeared to be the *anhydride* of anisyltrimethoxyphenylacrylic acid, into which it was converted by hydrolysis with alcoholic potash. It had m. p. 143—144° after three recrystallisations from acetone–light petroleum (Found: C, 68·2, 67·95; H, 5·9, 5·8. $C_{38}H_{38}O_{11}$ requires C, 68·0; H, 5·7%). This substance could be recrystallised without change from boiling alcohol.

α-p-*Anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*propionic Acid* (II; R = OMe, X = CO_2H).—The foregoing acrylic acid (3·7 g.) was hydrogenated in acetic acid (100 c.c.) with platinum oxide (0·2 g.) at 60—70°. The saturated *acid*, after three recrystallisations from aqueous methyl alcohol, formed a colourless microcrystalline powder (2·9 g.), m. p. 95·5—96·5° (Found: C, 65·7; H, 6·3. $C_{19}H_{22}O_6$ requires C, 65·9; H, 6·4%). Its p-*phenylphenacyl* ester formed colourless fine needles, m. p. 94—95° (Found: C, 73·4; H, 5·9. $C_{33}H_{32}O_7$ requires C, 73·3; H, 6·0%).

α-*Cyano*-α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (I; R = OMe, X = CN).—Aqueous sodium hydroxide (1 g. in 5 c.c.) was added to a solution of 3 : 4 : 5-trimethoxybenzaldehyde (4·9 g.) and *p*-anisylacetonitrile (3·7 g.) in alcohol (7 c.c.). On slight warming, the condensation product began to crystallise, and was collected after cooling. α-*Cyano*-α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethylene* (8·1 g.) formed colourless leaflets with a violet fluorescence (from alcohol), m. p. 114—115° (Found: C, 70·2; H, 5·9. $C_{19}H_{19}O_4N$ requires C, 70·1; H, 5·9%).

β-p-*Anisyl*-γ-(3 : 4 : 5-*trimethoxyphenyl*)*propylamine*.—A solution of the aforesaid nitrile (16·2 g.) in alcohol (200 c.c.) was shaken at 60—70° with platinum oxide (0·4 g.) and hydrogen for 43 hours. The product was dissolved in ether and extracted with dilute hydrochloric acid to separate basic substances from neutral reduction products. The neutral ethereal solution gave 2·7 g. of α-*cyano*-α-p-*anisyl*-β-(3 : 4 : 5-*trimethoxyphenyl*)*ethane* (II; R = OMe, X = CN), which formed colourless rectangular plates, m. p. 96·5—97·5° (Found: C, 69·6; H, 6·6. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·5%). Hydrolysis with alcoholic alkali gave the *p*-anisyltrimethoxyphenylpropionic acid described above. This specimen had m. p. 97—98·5°.

The basic hydrogenation product was liberated from the hydrochloric acid extract and heated on the water-bath for 1½ hours with acetic anhydride (40 c.c.). The twice-distilled acetyl compound (5·9 g.; b. p. 258—263°/0·8 mm.), probably largely diacetyl compound, was refluxed for 4 hours with 10% alcoholic potash to convert it into the monoacetyl compound. The resulting N-*acetyl*-β-p-*anisyl*-γ-(3 : 4 : 5-*trimethoxyphenyl*)*propylamine* (III) crystallised from benzene–light petroleum in microscopic prisms, m. p. 124·5—125·5° (Found: C, 67·8, 67·7; H, 7·5, 7·4; N, 3·8; OMe, 31·95. $C_{21}H_{27}O_5N$ requires C, 67·5; H, 7·3; N, 3·75; OMe, 33·25%).

In another hydrogenation of the nitrile the crude amine, which solidified but could not be recrystallised, was further characterised by its p-*toluenesulphonyl* derivative, which crystallised from aqueous methyl alcohol in clumps of colourless needles, m. p. 135—136° (Found: C, 64·2; H, 6·6; S, 7·0. $C_{26}H_{31}O_6NS$ requires C, 64·3; H, 6·4; S, 6·7%), and its β-*naphthalenesulphonyl* derivative, which separated from methyl alcohol in colourless fine needles, m. p. 129·5—131° (Found: C, 66·85; H, 6·2; S, 6·35. $C_{29}H_{31}O_6NS$ requires C, 66·8; H, 6·0; S, 6·15%).

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