Synthesis and Antiinflammatory Activity of 5-Substituted 2,3-Bis(*p*-methoxyphenyl)indoles

GILBERT A. YOUNGDALE, E. MYLES GLENN, DANIEL LEDNICER, AND JACOB SZMUSZKOVICZ

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

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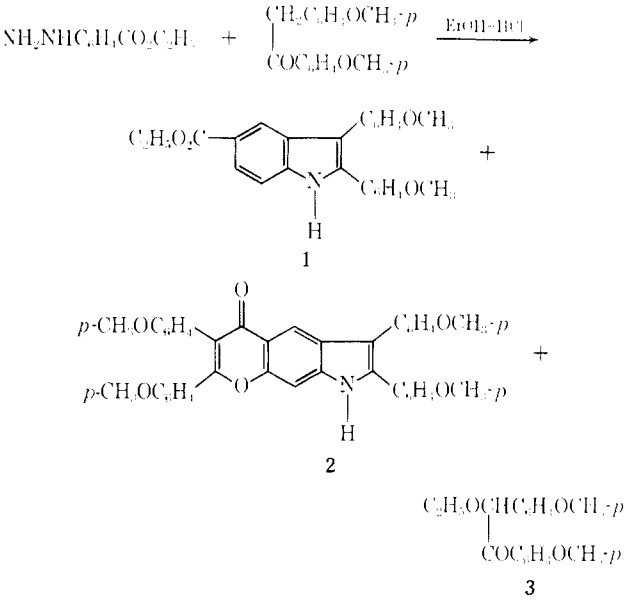
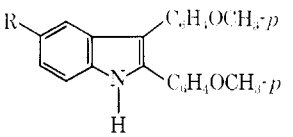
In a previous paper[1] the synthesis and antiinflammatory activity of 2,3-bis(*p*-methoxyphenyl)indole and related compounds were reported. As an extension of this work we now are reporting on additional derivatives of 2,3-bis(*p*-methoxyphenyl)indole, namely, the 5-carboxylic acid and the corresponding ethyl and hydroxyethyl esters, and the 5-acetyl compound.

The Fischer indole synthesis utilizing *p*-carbethoxyphenylhydrazine and desoxyanisoin was carried out in two ways. Using the acid-catalyzed procedure with ethanolic HCl led to ethyl 2,3-bis(*p*-methoxyphenyl)indole-5-carboxylate (**1**), 2,3,6,7-tetrakis(*p*-methoxyphenyl)pyrano[3,2-*f*]indol-4-(8H)-one (**2**), and 2-ethoxy-4′-methoxy-2-(*p*-methoxyphenyl)acetophenone (**3**) (Scheme I). On the other hand, the noncatalyzed

SCHEME I

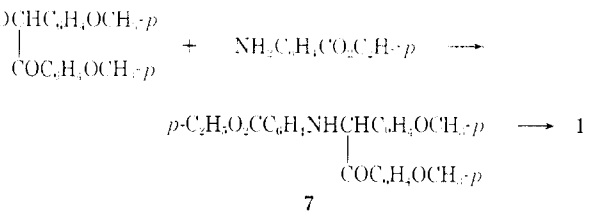


procedure with ethylene glycol as the solvent produced 2-hydroxyethyl 2,3-bis(*p*-methoxyphenyl)indole-5-carboxylate (**4**).



4. R = $CO_2CH_2CH_2OH$
5. R = CO_2H
6. R = $COCH_3$

Compound **1** was also prepared from anisoin and ethyl *p*-aminobenzoate *via* ethyl *p*-{[*p*-methoxy-α-(*p*-methoxyphenyl)phenacyl]amino}benzoate (**7**).



Saponification of **1** or **4** produced 2,3-bis(*p*-methoxyphenyl)indole-5-carboxylic acid (**5**). This was converted to the acid chloride which was treated with dimethylcadmium to produce 5-acetyl-2,3-bis(*p*-methoxyphenyl)indole (**6**).

Compounds **1** and **4**–**6** were tested for antiinflammatory activity using Polysorbate 80 as the vehicle as previously described.[1] Only **6** showed significant activity, equal to 2,3-bis(*p*-methoxyphenyl)indole.[1]

Experimental Section[2]

Ethyl *p*-{[*p*-Methoxy-α-(*p*-methoxyphenyl)phenacyl]amino}-benzoate (7).—A mixture of 27.2 g (0.1 mole) of anisoin, 16.5 g (0.1 mole) of ethyl *p*-aminobenzoate, a few crystals of *p*-TsA, and 500 ml of xylene was refluxed for 2 hr using a water separator. The cooled solution was washed (dilute HCl, H_2O, dilute Na_2CO_3, H_2O), dried ($MgSO_4$), and evaporated. The resulting solid was crystallized from Me_2CO–Skellysolve B to give 33.8 g (81%), mp 137–140°, raised to 140.5–141.5° after two recrystallizations. *Anal.* ($C_{25}H_{25}NO_5$) C, H, N.

Ethyl 2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylate (1).—A mixture of 13 g (31 mmoles) of **7**, 8.26 g (5 mmoles) of ethyl *p*-aminobenzoate, and 2 drops of concentrated HCl was heated at 200–205° (oil-bath temperature) for 5 hr. A solution of the cooled mixture in CH_2Cl_2 was washed twice with dilute HCl and dried ($MgSO_4$). Evaporation of the CH_2Cl_2 left 11.6 g of brown tar. The tar was chromatographed on silica gel using 2% Me_2CO in CH_2Cl_2 as the eluent. Crystallization from Me_2CO–Skellysolve B of those fractions which were pure by tlc gave 4.1 g (33%) of **1**, mp 194–197°, raised to 201–202° by recrystallization. *Anal.* ($C_{25}H_{23}NO_4$) C, H, N.

Ethyl 2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylate (1), 2,3,6,7-Tetrakis(*p*-methoxyphenyl)pyrano[3,2-*f*]indol-4(8H)-one (2), and 2-Ethoxy-4′-methoxy-2-(*p*-methoxyphenyl)acetophenone (3).—A mixture of 18.0 g (0.1 mole) of *p*-carbethoxyphenylhydrazine[3] and 25.6 g (0.1 mole) of desoxyanisoin was stirred and heated at 160–170° (internal) for 10 min. After cooling 250 ml of 3 *N* ethanolic HCl was added. The mixture was refluxed for 3 hr and then allowed to stand for 3 days. The resulting suspension was filtered (filtrate A). The solid was crystallized from CH_2Cl_2, filtered, and washed with H_2O to give 1.3 g of **2**, mp 271–272°. The analytical sample, mp 272–273°, was obtained by two crystallizations from CH_2Cl_2; mass spectroscopic mol wt, 609. *Anal.* ($C_{39}H_{31}NO_6$) C, H, N.

Filtrate A was evaporated, and the residue was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with 5% HCl, 5% NaOH, and saturated NaCl solution. It was then dried (Na_2SO_4) and evaporated. The residue was chromatographed on 2.2 kg of silica gel using 20% EtOAc in cyclohexane as the eluent and collecting 400-ml fractions. Fractions 23–29

(1) J. Szmuszkovicz, E. M. Glenn, R. V. Heinzelman, J. B. Hester, Jr., and G. A. Youngdale, *J. Med. Chem.*, **9**, 527 (1966).

(2) Melting points were taken in open glass capillaries using a Thomas–Hoover Uni-Melt apparatus and are recorded as obtained. Ir, uv, and nmr spectra were obtained for all the compounds. Ir spectra were determined in Nujol using a Perkin-Elmer recording ir spectrophotometer Model 21. Uv spectra were determined in 95% EtOH using a Cary spectrophotometer Model 14. The nmr spectra were measured at 60 Mc. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Florisil is magnesia–silica gel adsorbent manufactured by Floridin Co., Pittsburgh, Pa.

(3) N. K. Kochetkov, N. F. Kucherova, L. P. Pronina, and M. I. Petrushenko, *J. Gen. Chem. USSR*, **29**, 3581 (1959).

were crystallized from MeOH to give a solid which was washed with Et_2O. Three crystallizations from Et_2O gave 0.75 g of **3**, mp 101–103°. It was identified by spectral comparison with an authentic sample.[4]

Fractions 38–52 were crystallized from MeOH to give 2 g of **1**, mp 201–202°. It was identical with authentic **1** previously prepared.

2-Hydroxyethyl 2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylate (4).—A mixture of 29.1 g (0.16 mole) of *p*-carbethoxyphenylhydrazine[3] and 41.5 g (0.16 mole) of desoxyanisoin was stirred and heated at 160–170° (internal) for 10 min. Ethylene glycol (485 ml) was added and the mixture was refluxed for 22 hr. The solid obtained upon cooling and filtration was crystallized from EtOH to give 31.7 g (47%) of **4**, mp 209–210°, raised to 211–212° on recrystallization. *Anal.* ($C_{25}H_{23}NO_5$) C, H, N.

2,3-Bis(*p*-methoxyphenyl)indole-5-carboxylic Acid Acetone Solvate (5).—A mixture of 11 g of **4**, 20 g of KOH, 80 ml of H_2O, and 200 ml of EtOH was refluxed for 18 hr. The EtOH was evaporated. A solution of the residue in H_2O was extracted with Et_2O and was then acidified with concentrated HCl. The solid obtained was crystallized from Me_2CO–H_2O to give 9 g (79%) of **5**, mp 296–298° dec, raised to 297–298° by crystallization from Me_2CO–Skellysolve B. *Anal.* ($C_{23}H_{19}NO_4 \cdot C_3H_6O$) C, N; H: calcd, 5.84; found, 6.31.

Saponification of **1** also gave **5**.

5-Acetyl-2,3-bis(*p*-methoxyphenyl)indole (6).—A mixture of 1 g of **5**, 10 ml of $SOCl_2$, and 25 ml of C_6H_6 was refluxed for 1 hr and then evaporated to give the acid chloride. A solution of 6 ml of 3 *M* ethereal MeMgBr in 50 ml of Et_2O was added to a stirred suspension of 1.80 g of $CdCl_2$ in 20 ml of Et_2O. The resulting suspension was cooled in ice and a solution of the acid chloride in 25 ml of Et_2O was added. The mixture was refluxed for 4 hr, cooled in ice, treated with 50 ml of 2.5 *N* HCl, and extracted with CH_2Cl_2. The extract was washed with H_2O, 1 *N* NaOH, and H_2O and evaporated. The resulting solid was chromatographed on Florisil using 8% Me_2CO in Skellysolve B as the eluent. The solid fractions were crystallized twice from EtOAc to give 0.25 g (29%) of **6**, mp 222–223°. *Anal.* ($C_{24}H_{21}NO_3$) C, H, N.

(4) J. C. Irvine and D. McNicoll, *J. Chem. Soc.*, **93**, 1601 (1908).

Antimalarials. Chloroquine Analogs with the 1,2,3,6-Tetrahydropyridyl Function in the Side Chain

TARA SINGH, ROBERT G. STEIN, AND JOHN H. BIEL

Research Laboratories, Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53210

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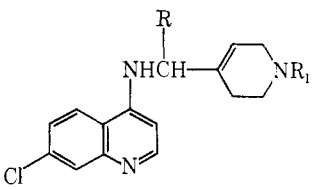
In a recent publication, Bailey[1] has reported "folded" chloroquine analogs of the structure **1** (saturated



1a, R = H; $R_1 = CH_3$
b, R = CH_3; $R_1 = CH_3$
c, R = CH_3; $R_1 = C_2H_5$

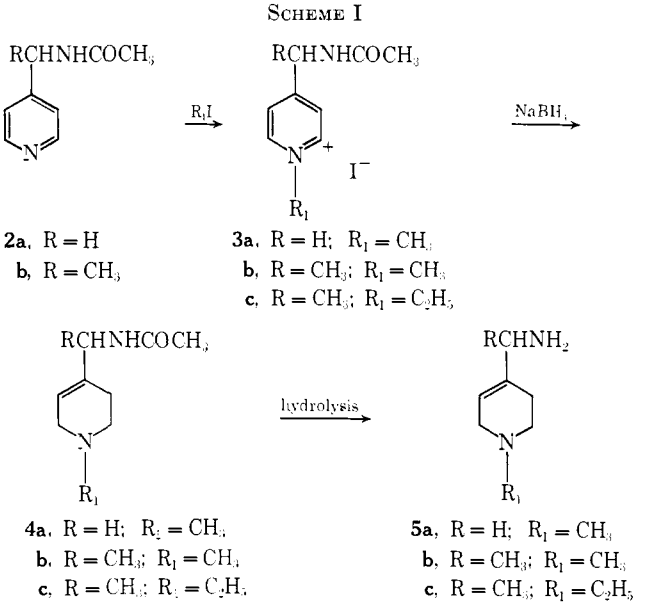
pyridyl ring) where R = H and CH_3 and $R_1 = C_2H_5$ and CH_2CH_2OH. This has prompted us to report a few similar compounds but with a double bond between C-4 and C-5 as shown in the generic structure **1** (see Table I).

(1) D. M. Bailey, *J. Med. Chem.*, **12**, 184 (1969).

The rationale for making such compounds was arrived at from several publications[2] in which a number of compounds containing the 1,2,3,6-tetrahydropyridyl moiety have been reported to exhibit promising pharmacological activity. Furthermore, we have found earlier[3] that the introduction of an unsaturation function such as the *cis* and *trans* double bond and an acetylenic triple bond in the chloroquine side chain significantly improved the antimalarial activity and lowered the toxicity when tested against *Plasmodium berghei* in mice. Thus, 1,2,3,6-tetrahydropyridyl moiety presented a unique feature containing a modified cyclic chloroquine side chain as well as one unsaturated center.

The tetrahydropyridylamines were made as outlined in Scheme I. The general procedures are described in

SCHEME I



the Experimental Section. It is well known that the reduction of pyridinium salts with KBH_4[4] and $NaBH_4$[5] gives 1,2,3,6-tetrahydropyridyl compounds. On the basis of this accumulated evidence, the amines have been assigned the structure as shown.

Biological Activity.—The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice. The screening was carried out by Dr. L. Rane of the University of Miami, Miami, Fla., according to the procedure published by Osdene, Russell, and Rane.[6] The activity figures are given in Table II.

Experimental Section

Acetylaminoalkylpyridines (2) were prepared by the reaction of excess Ac_2O with aminopyridines.

(2) J. H. Biel and H. B. Hopps, U. S. Patent 3,221,019 (1965); *Chem. Abstr.*, **64**, 5053*e* (1966); French Patent M3502 (1965); *Chem. Abstr.*, **64**, 2104*d* (1966); J. R. Geigy A.G., Netherlands Appl 6,408,219 (1965); *Chem. Abstr.*, **63**, 586*a* (1965); F. Hoffmann-La Roche & Co. A.G., Netherlands Appl 6,407,413 (1965); *Chem. Abstr.*, **63**, 1774*b* (1965), and Netherlands Appl 6,407,463 (1965); *Chem. Abstr.*, **62**, 16207*c* (1965).

(3) T. Singh, R. G. Stein, and J. H. Biel, *J. Med. Chem.*, **12**, 368 (1969).

(4) J. J. Panouse, *Compt. Rend.*, **233**, 260, 1200 (1951); *Chem. Abstr.*, **46**, 2542*i*, 6643*h* (1952).

(5) R. E. Lyle, E. F. Perlowski, H. J. Troscianiec, and G. G. Lyle, *J. Org. Chem.*, **20**, 1761 (1955); R. C. Elderfield, B. Fischer, and J. M. Lagowski, *ibid.*, **22**, 1376 (1957); E. Wenkert, R. A. Massey-Westrop, and R. G. Lewis, *J. Amer. Chem. Soc.*, **84**, 3732 (1962).

(6) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).