

Synthesis of Derivatives of the New Heterocyclic Systems Benz[*f*]imidazo[2,1-*a*]isoquinoline and Benz[*f*]pyrimido[2,1-*a*]isoquinoline

C. Avellana, V. Gómez-Parra (1) and R. Madroñero

Instituto de Química Médica, Juan de la Cierva 3, Madrid-6, Spain

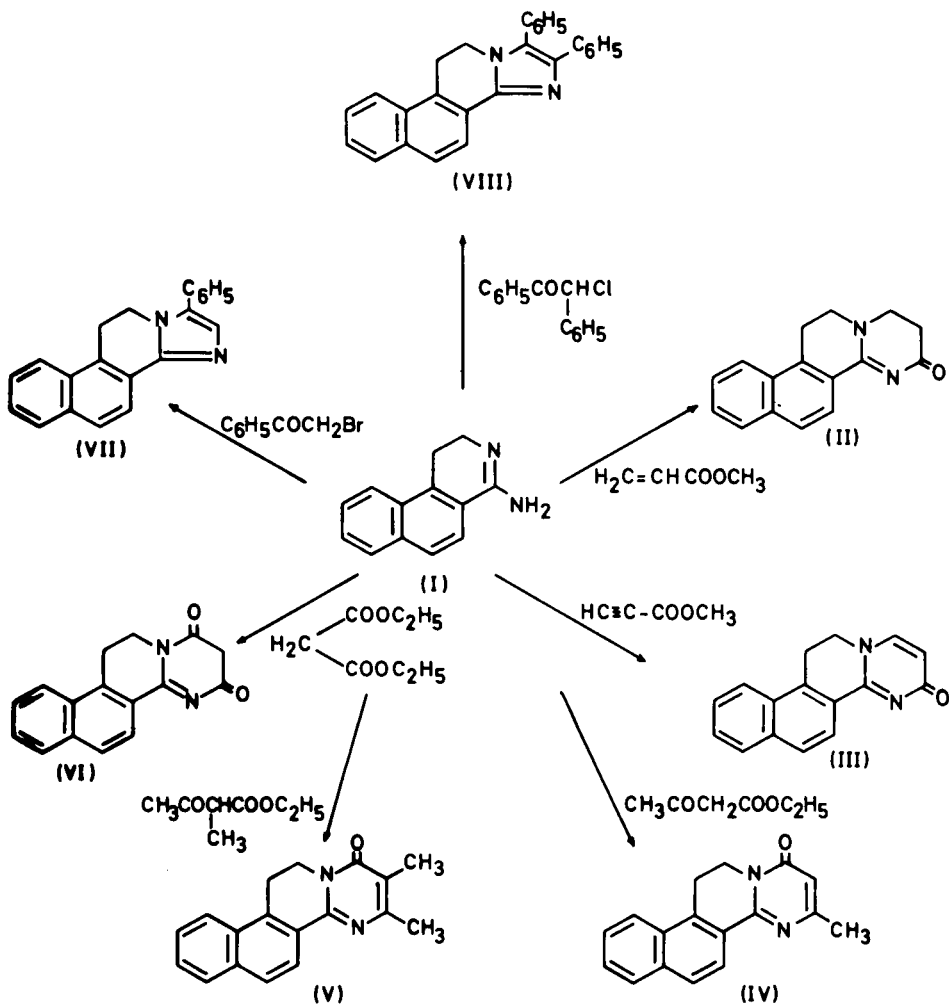
Received November 22, 1976

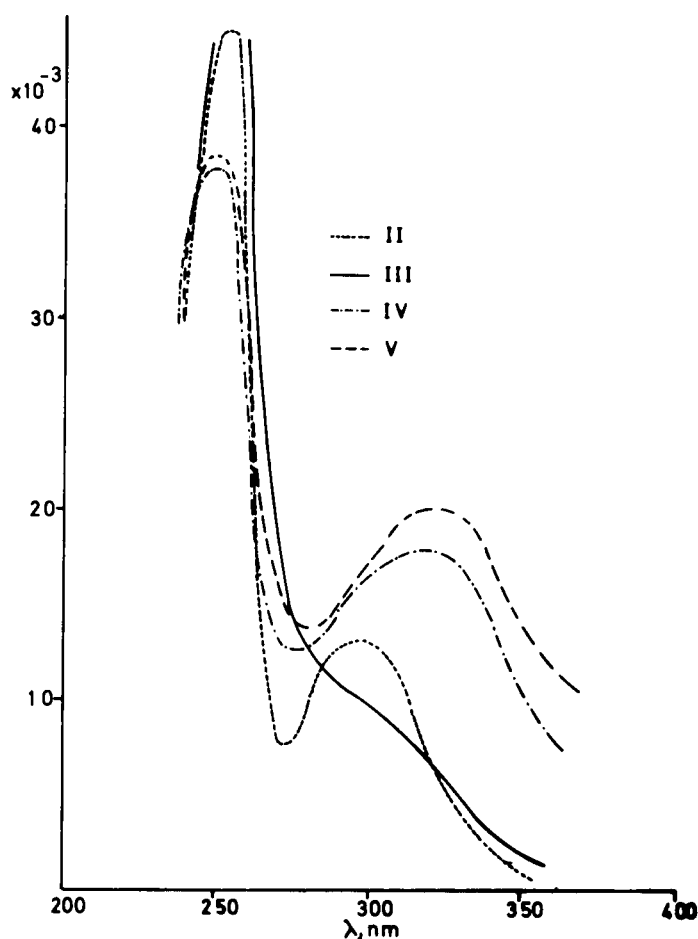
The synthesis of several derivatives of benz[*f*]imidazo[2,1-*a*]isoquinoline and benz[*f*]pyrimido[2,1-*a*]isoquinoline, both new heterocyclic structures, is described.

J. Heterocyclic Chem., 14, 325 (1977).

As a part of our program on the synthesis of azasteroids, we report here the preparation of several derivatives of benz[*f*]imidazo[2,1-*a*]isoquinoline and benz[*f*]pyrimido[2,1-*a*]isoquinoline, which are new heterocyclic structures.

The starting material for these synthesis is the 4-amino-1,2-dihydrobenz[*f*]isoquinoline I (2) obtained by nucleophilic substitution with ammonia from the 4-thioalkyl-1,2-dihydrobenz[*f*]isoquinoline (3). Compound I reacts





with several reactives, as described in the scheme to afford the expected compounds in good yields.

In the case of the reaction between I and ethyl acetoacetate or ethyl-2-methyl acetoacetate two regioisomers could be expected but only one was isolated. Assignment of the position of the C=O group in the compounds IV and V has been established by their ultraviolet (uv) absorption spectra, on the basis of Adams and Pachter work (4), who found in the uv spectra of series of pyrido[1,2-*a*]pyrimidin-2-ones and pyrido[1,2-*a*]pyrimidin-4-ones low ϵ values in the 320-360 $m\mu$ zone for the 2-one compounds and high ϵ values for the 4-one derivatives.

In the uv spectra of our compounds II, III, IV and V (Figure) a clear difference is observed between the spectra of compounds II and III and that of compounds IV and V. The high ϵ values found in the zone 320-360 nm for compounds IV and V are according with the assigned structures.

On the other hand, Kato, *et al.*, (5) found that the product obtained by reaction of 2-aminopyridine and diketene is 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and not the 2-one derivative. The fact that the reaction of

compound I and diketene affords only compound IV, seems to confirm the assignment made of the C-O group position in these compounds.

EXPERIMENTAL

Melting points were determined in capillary tubes (Gallenkamp melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide disks using a Perkin-Elmer 257 spectrophotometer. Uv absorption spectra were measured in methanol with a Perkin-Elmer 350 spectrometer and nmr spectra by a Perkin-Elmer R-12 instrument at 60 MHz, with TMS as an internal standard.

The chemical shifts are given in δ units.

3-Oxo-1,2,11,12-tetrahydro-3*H*-benz[*f*]pyrimido[2,1-*a*]isoquinoline (II).

A suspension of 1.96 g. (0.01 mole) of I and 0.86 g. (0.01 mole) of methyl acrylate in benzene (30 ml.) was heated under reflux. In five minutes the solid disappeared and instantaneously a new white solid precipitated, which was filtered and recrystallized from dimethyl sulfoxide, yield, 1.6 g. (65%) of product, m.p. 246-248°; ir: 1660 cm^{-1} (C=O); uv λ max nm ($\epsilon \times 10^{-3}$): 259 (45.8); 270 (71.0); 297 (18.4); nmr (trifluoroacetic acid-*d*): 8.4-7.8 (multiplet, 5H, 6H, 7H, 8H, 9H, 10H); 4.45 (t, 12-H); 4.30 (t, 1-H); 3.90 (t, 2-H) and 3.35 (t, 11-H).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.63; N, 11.20. Found: C, 76.97; H, 5.68; N, 11.15.

3-Oxo-11,12-dihydro-3*H*-benz[*f*]pyrimido[2,1-*a*]isoquinoline (III).

A mixture of 1.96 g. (0.01 mole) of I, 0.84 g. (0.01 mole) of methyl propylate and 30 ml. of ethanol was refluxed for 1 hour. When the solution was cooled a white solid crystallized. Recrystallization from *N,N*-dimethylformamide afforded 1.25 g. (50%) of product, m.p. 293-294°; ir: 1658 cm^{-1} (C=O); uv λ max nm ($\epsilon \times 10^{-3}$): 252 (59.4); 260 (69.2); 296 (11.6); nmr (trifluoroacetic acid-*d*): 8.37 (d, 1-H); 8.00 (multiplet, 5H, 6H, 7H, 8H, 9H, 10H); 7.12 (d, 2-H); 4.82 (t, 12-H) and 4.03 (t, 11-H).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.41; H, 4.83; N, 11.28. Found: C, 77.52; H, 4.91; N, 11.20.

1-Oxo-3-methyl-11,12-dihydro-1*H*-benz[*f*]pyrimido[2,1-*a*]isoquinoline (IV).

A mixture of 0.98 g. (0.005 mole) of I, 0.65 g. (0.005 mole) of ethyl acetoacetate and 20 ml. of ethanol was refluxed for 2 hours. Once the solution cooled, a white solid crystallized which was recrystallized from methanol yielding 0.9 g. (70%) of IV, m.p. 175-176°; ir: 1680 cm^{-1} (C=O); uv λ max nm ($\epsilon \times 10^{-3}$): 251 (38.3); 257 (34.1); 319 (18.2); nmr (chloroform): 8.2-7.4 (multiplet, 5H, 6H, 7H, 8H, 9H, 10H); 6.22 (s, 2-H); 4.30 (t, 12-H); 3.32 (t, 11-H) and 2.30 (s, 3-CH₃).

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.37; N, 10.68. Found: C, 77.79; H, 5.40; N, 10.68.

1-Oxo-2,3-dimethyl-11,12-dihydro-1*H*-benz[*f*]pyrimido[2,1-*a*]isoquinoline (V).

A mixture of 0.98 g. (0.005 mole) of I, 0.72 g. (0.005 mole) of ethyl-2-methyl-acetoacetate and 20 ml. of ethanol was heated and when the boiling temperature was reached the product of reaction suddenly crystallized, which was filtered and recrystallized from 2-propanol to afford 1 g. of product (72%), m.p. 201-202°; ir: 1670 cm^{-1} (C=O); uv λ max nm ($\epsilon \times 10^{-3}$): 250 (38.9); 260 (29.2); 325 (20.7); nmr (chloroform): 8.5-7.3 (multiplet, 5H,

6H, 7H, 8H, 9H, 10H); 4.41 (t, 12-H); 3.42 (t, 11H); 2.40 (s, 3-CH₃) and 2.15 (s, 2-CH₃).

Anal. Calcd. for C₁₈H₁₆N₂O: C, 78.26; H, 5.79; N, 10.13. Found: C, 78.27; H, 5.77; N, 10.10.

1,3-Dioxo-1,2,11,12-tetrahydro-3H-benz[*f*]pyrimido[2,1-*a*]isoquinoline (VI).

A suspension of 0.98 g. (0.005 mole) of I and 0.8 g. (0.005 mole) of diethyl malonate in *o*-dichlorobenzene (20 ml.) was heated under reflux for 2 hours. When the solution was cooled a white solid crystallized which was purified from *o*-dichlorobenzene to yield 0.6 g. (45%) of product, m.p. 301-302°; ir: 1650 cm⁻¹; nmr (trifluoroacetic acid-*d*): 8.48-7.62 (multiplet, 5H, 6H, 7H, 8H, 9H, 10H); 6.37 (s, 2-CH₂); 4.72 (t, 12-H) and 3.80 (t, 11-H).

Anal. Calcd. for C₁₆H₁₂N₂O₂: C, 72.71; H, 4.54; N, 10.60. Found: C, 72.68; H, 4.57; N, 10.54.

1-Phenyl-10,11-dihydrobenz[*f*]imidazo[2,1-*a*]isoquinoline (VII).

A mixture of 1.96 g. (0.01 mole) of I, 1.99 (0.01 mole) of phenacyl bromide and 0.84 g. of sodium hydrogen carbonate in ethanol (25 ml.) was stirred at room temperature for 3 hours and then poured into ice-water. The solid was filtered and recrystallized from acetonitrile to afford 1.95 g. (65%) of product, m.p. 241-243°; nmr (trifluoroacetic acid-*d*): 8.10-7.50 (multiplet, 1-C₆H₅, 2H, 4H, 5H, 6H, 7H, 8H, 9H); 4.62 (t, 11-H) and 3.80 (t, 10-H).

Anal. Calcd. for C₂₁H₁₆N₂: C, 85.13; H, 5.40; N, 9.45.

Found: C, 85.06; H, 5.43; N, 9.42.

1,2-Diphenyl-10,11-dihydrobenz[*f*]imidazo[2,1-*a*]isoquinoline (VIII).

This compound was obtained from 1.96 g. (0.01 mole) of I, 2.3 g. (0.01 mole) of α -chloro- α -phenylacetophenone and 0.64 g. of sodium hydrogen carbonate in 20 ml. of ethanol, as described for compound VII. Recrystallization from *N,N*-dimethylformamide yielded 2.39 g. (40%) of product, m.p. 214-216°; nmr (trifluoroacetic acid-*d*): 7.95-7.10 (multiplet, 1-C₆H₅; 2-C₆H₅, 4H, 6H, 7H, 8H, 9H); 4.05 (t, 11-H) and 3.42 (t, 10-H).

Anal. Calcd. for C₂₇H₂₀N₂: C, 87.09; H, 5.37; N, 7.52. Found: C, 86.94; H, 5.42; N, 7.49.

REFERENCES AND NOTES

- (1) To whom correspondence should be addressed.
- (2) C. Avellana, V. Gómez-Parra and R. Madroñero, *Synthesis*, 252 (1976).
- (3) M. Lora-Tamayo, R. Madroñero, D. Gracián and V. Gómez-Parra, *Tetrahedron*, Suppl. 8, Part I, 305 (1966).
- (4) R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, 74, 5491 (1952).
- (5) T. Kato, H. Yamanaka, N. Katagiri and S. Masuda, *Chem. Pharm. Bull.*, 20, 142 (1972).