cooled, treated with EtOAc (10 ml), and refluxed for 30 min. After addn of H_2O and 1 *N* NaOH alternately, the mixt was filtered and concd *in vacuo* to remove THF. The residue was acidified with 6 *N* HCl and extd with Et_2O. The aq acid soln was basified and extd with Et_2O, and the dried Et_2O ext was treated with ethanolic HCl to afford 0.51 g (yield, 78%) of 8·HCl.

(+)-3-Hydroxymorphinan (12). A $CHCl_3$ soln (25 ml) contg 4.0 g (0.0015 mole) of 7 was treated with ethyl chloroformate (20 ml) and anhyd K_2CO_3 (2 g). The reaction mixt was stirred for 24 hr and the $CHCl_3$ then removed *in vacuo*. The residue was suspended in 1 *N* HCl (50 ml) and extd with Et_2O. Removal of Et_2O afforded an oil (2.5 g) which was dissolved in a mixt of glacial AcOH (10 ml) and 48% HBr (10 ml). After refluxing under N_2 for 6 hr, the reaction mixt was poured in ice water (300 ml), extd with Et_2O, and basified to afford 1.1 g (31%) of 12, mp 260–263° [reported for (−)-3-hydroxymorphinan, mp 260–262°].[18]

Norcodeine (7). A soln of 3.8 g (0.012 mole) of codeine (4) in $CHCl_3$ (50 ml) was treated with ethyl chloroformate (5 ml) and 15% aq KOH (50 ml). The 2-phase reaction mixt was shaken for 24 hr. Five successive 1-ml portions of ethyl chloroformate were added to the reaction mixt at 1-hr intervals, and KOH soln was added when necessary to maintain a pH > 10. At the end of 24 hr, the $CHCl_3$ layer was sepd and extd with 1 *N* HCl. The $CHCl_3$ was removed *in vacuo* to afford an oil (3.2 g) whose ir spectrum included characteristic absorptions at 1690 cm^{-1} (C=O of N-CO_2Et) and 1740 cm^{-1} (C=O of O^6-CO_2Et). This was treated with a mixt of MeOH (90 ml) and 10% aq K_2CO_3 (10 ml) for 2 hr, concd *in vacuo* to remove MeOH, extd with Et_2O, and the Et_2O was extd with 1 *N* HCl. Removal of Et_2O afforded 2.5 g of an oily uncrystallizable material. A soln of 2.0 g of the oil in 95% EtOH (80 ml) was treated with 50% aq KOH (20 ml) and refluxed under N_2 for 24 hr. The soln was dild with H_2O (20 ml) and the EtOH was removed under reduced pressure. The aq acid soln was basified and extd with Et_2O. The Et_2O was removed under reduced pressure to give 0.7 g (yield, 43%) of 7: mp 183–185° (reported mp 185°);[19] 7·HCl, mp 309–311° dec (reported mp 309° dec).[19]

References

(1) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966).
(2) "Analgetics," G. deStevens, Ed., Academic Press, New York, N. Y., 1965.
(3) H. A. Hageman, *Org. React.*, 7, Chapter 4 (1953).
(4) O. Diels and E. Fischer, *Ber.*, **47**, 2043 (1914).
(5) A. Pohland and H. R. Sullivan, Jr., U. S. Patent 3,342,824 (1967).
(6) E. Speyer and L. Walther, *Ber.*, **69B**, 852 (1930).
(7) E. Späth, L. Marion, and E. Zajic, *ibid.*, **69B**, 251 (1936).
(8) F. Bayer and Co., German Patent 255,942 (1911).
(9) J. Gadamer and F. Knoch, *Arch. Pharm. (Weinheim)*, **259**, 135 (1921).
(10) E. H. Flynn, H. W. Murphy, and R. D. McMahon, *J. Amer. Chem. Soc.*, **77**, 3104 (1955).
(11) J. A. Campbell, *J. Org. Chem.*, **22**, 1259 (1957).
(12) M. M. Abdel-Monem and T. O. Soine, *J. Pharm. Sci.*, **56**, 976 (1967).
(13) G. Kraiso and L. Nador, *Tetrahedron Lett.*, **57** (1971).
(14) J. D. Hobson and J. B. McCluskey, *J. Chem. Soc.*, 15 (1967).
(15) R. E. McMahon in "Advances in Tracer Methodology," Vol. 4, S. Rothchild, Ed., Plenum Press, New York, N. Y., 1968, p 29.
(16) Merck Index, 8th Ed., D. G. Stecher, Ed., Merck and Co., Inc., Rahway, N. J., 1968, p 702.
(17) Reference 16, p 749.
(18) O. Schnider and A. Grussner, *Helv. Chim. Acta*, 34, 2211 (1951).
(19) Reference 16, p 747.

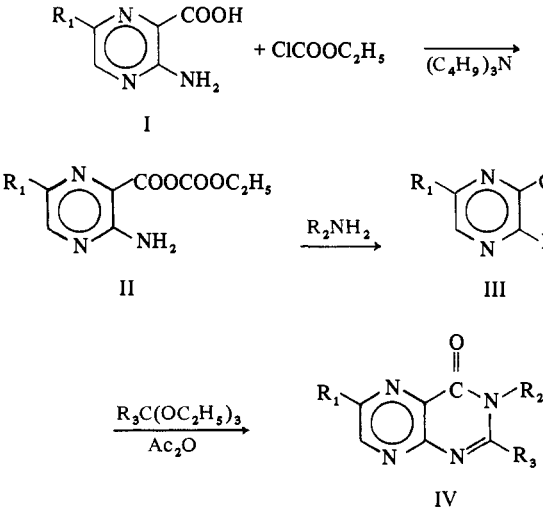
Synthesis of 4(3*H*)-Pteridinones

Ernst Felder,* Davide Pitrè, and Sergio Boveri

Research Laboratories, Bracco Industria Chimica, Milan, Italy.

Received May 24, 1971

The sedative-hypnotic activity of some 4(3*H*)-quinazolones[1] prompted us to synthesize a number of the isosteric 4(3*H*)-pteridinones and to investigate their hypnotic and sedative activities. The existing literature gives only a few examples of preparation of 3-alkyl or 3-aryl substituted 4(3*H*)-pteridinones[2-4] and no data at all on their pharmacology. The synthesis of the title compounds involved the intermediate 3-aminopyrazinecarboxamides, described in Table I, which were obtained, in good yield, from 3-aminopyrazinoic acid (I),[5] *via* the mixed anhydride (II)[6] and reaction of the latter with appropriate amines (R_2NH_2).



The 3-aminopyrazinecarboxamides (III) could be cyclized to the desired 4(3*H*)-pteridinones (IV) by condensation with an ortho ester $R_3C(OC_2H_5)_3$ in Ac_2O solution. The amides (III), in contrast to the 4(3*H*)-pteridinones (IV), reveal a characteristic fluorescence under uv light, which is helpful for their identification by chromatography.

In preliminary CNS screening the majority of the compounds were found to be without hypnotic or sedative activity. Compds **23**, **30**, and **31** showed a slight sedative activity at 300 mg/kg (mouse) and with **30**, **31**, and **38** some analgetic activity was observed at 150–250 mg/kg (mouse; phenylbenzoquinone test) and 150–500 mg/kg (mouse; hot-plate test), but all the compounds showed too low a therapeutic index, the LD_{50} (mg/kg; mouse; Litchfield and Wilcoxon) being 1250 (1042–1500), 575 (483–684), 1220 (1070–1391), and 1750 (1400–2187) for **23**, **30**, **31**, and **38**, respectively.

Experimental Section

The melting points of all but four compds 21–47 were taken with a Mettler FP-1 apparatus, all the others with a Büchi apparatus, and are uncorrected. Uv and ir spectra were measured for some typical compds and were as expected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

3-Aminopyrazinecarboxamides (1–20). A mixt of 5.56 g (0.04 mole) of 3-aminopyrazinoic acid, 7.4 g (0.04 mole) of Bu_3N, and 50 ml of dioxane was stirred at room temp until a clear soln resulted. This soln was cooled to 7–8° and 4 ml (0.04 mole) of EtOCOCl was added dropwise, keeping the temp at 11–12°. After cooling again to 7–8°, 0.04 mole of the appropriate amine hydrochloride was added, and the reaction was allowed to proceed at room temp for 3 hr. The solvent was removed on a rotatory evaporator under reduced pressure and the residue was triturated for 30 min with 50 ml of H_2O, filtered, dried, and recrystd. Recrystn solvents and physical data are given in Table I.

4(3*H*)-Pteridinones (21–47). A mixt of 0.01 mole of III, 25 ml of ortho ester, and 20–30 ml of Ac_2O was refluxed for 5 hr and then concd on a rotatory evaporator at room temp *in vacuo*. The residue was triturated with 20 ml of EtOH, and, after evapn of the solvent, washed with Et_2O, filtered, dried, and recrystd. Recrystn solvents and physical data are given in Table II. For **23** the reaction was carried out in anhyd HCO_2H, and for 24 in 1:1 anhyd HCO_2H-Ac_2O

Table I. 3-Aminopyrazinecarboxamides (III)

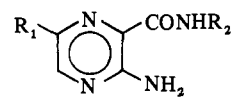
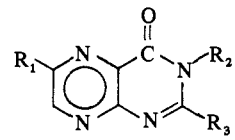
No.	R_2	R_1	Formula	Mp, °C	Crystn solvent	Anal.
						
1	CH_3	H	$C_6H_8N_4O$	134	33% EtOH	C, H, N
2	$CH(CH_3)_2$	H	$C_8H_{12}N_4O \cdot HCl \cdot H_2O$	134	EtOH	C, H, Cl, N, H_2O
3	Cyclo-C_5H_9	H	$C_{10}H_{14}N_4O$	73	EtOH-H_2O	C, H, N
4	Cyclo-C_6H_{11}	H	$C_{11}H_{16}N_4O$	107-108	33% EtOH	C, H, N
5	C_6H_5	H	$C_{11}H_{10}N_4O$	105	50% EtOH	C, H, N
6	*o*-$CH_3C_6H_4$	H	$C_{12}H_{12}N_4O$	136	50% EtOH	C, H, N
7	*m*-$CH_3C_6H_4$	H	$C_{12}H_{12}N_4O$	112	50% EtOH	C, H, N
8	*p*-$CH_3C_6H_4$	H	$C_{12}H_{12}N_4O$	158	EtOH	C, H, N
9	*o*-(*i*-Pr)C_6H_4	H	$C_{14}H_{16}N_4O$	154	95% EtOH	C, H, N
10	*p*-(*i*-Pr)C_6H_4	H	$C_{14}H_{16}N_4O$	125	95% EtOH	C, H, N
11	*o*-$EtOC_6H_4$	H	$C_{13}H_{14}N_4O_2$	134-135	65% EtOH	C, H, N
12	*m*-$EtOC_6H_4$	H	$C_{13}H_{14}N_4O_2$	104-105	65% EtOH	C, H, N
13	*p*-$EtOC_6H_4$	H	$C_{13}H_{14}N_4O_2$	139-140	65% EtOH	C, H, N
14	*p*-$BuOC_6H_4$	H	$C_{15}H_{18}N_4O_2$	134	EtOH	C, H, N
15	*p*-$C_6H_4O(CH_2)_2C_6H_5$	H	$C_{19}H_{18}N_4O_2$	180	*n*-BuOH	C, H, N
16	$CH(C_6H_5)CH_2(C_6H_5)$	H	$C_{19}H_{18}N_4O$	136	95% EtOH	C, H, N
17	*p*-ClC_6H_4	H	$C_{11}H_9ClN_4O$	190-191	Dioxane-H_2O	C, H, Cl, N
18	3-Pyridyl	H	$C_{10}H_9N_5O$	155-156	EtOH	C, H, N
19	C_6H_5	Br	$C_{11}H_9BrN_4O$	157	95% EtOH	C, H, Br, N
20	*o*-$CH_3C_6H_4$	Br	$C_{12}H_{11}BrN_4O$	176	95% EtOH	C, H, Br, N

Table II. 4(3*H*)-Pteridinones (IV)

No.	R_2	R_3	R_1	Formula	Mp, °C	Crystn solvent[a]	Anal.
							
21	CH_3	H	H	$C_7H_6N_4O$	294.5-296.5	MeCN	C, H, N
22	$CH(CH_3)_2$	H	H	$C_9H_{10}N_4O$	204.5-207	EtOH	C, H, N
23	*o*-$CH_3C_6H_4$	H	H	$C_{13}H_{10}N_4O$	166.5-172.5	C_6H_6-P	C, H, N
24	*m*-$CH_3C_6H_4$	H	H	$C_{13}H_{10}N_4O$	235-236.5	$CHCl_3$-Et_2O	C, H, N
25	*p*-$C_2H_5OC_6H_4$	H	H	$C_{14}H_{12}N_4O_2$	239-241.5	MeCN	H, N, C[b]
26	*o*-$CH_3C_6H_4$	H	Br	$C_{13}H_9BrN_4O$	~147[d]	EtOH	C, H, Br, N
27	H	CH_3	H	$C_7H_6N_4O$	>299	MeCN	C, H, N
28	$CH(CH_3)_2$	CH_3	H	$C_{10}H_{12}N_4O$	202-205.5	THF	C, H, N
29	Cyclo-C_5H_9	CH_3	H	$C_{12}H_{14}N_4O$	164.5-167	*n*-Bu_2O	C, H, N
30	Cyclo-C_6H_{11}	CH_3	H	$C_{13}H_{16}N_4O$	203-204.5	C_6H_6-P	C, H, N
31	*o*-$CH_3C_6H_4$	CH_3	H	$C_{14}H_{12}N_4O$	188.5-190.5	C_6H_6-P	C, H, N
32	*m*-$CH_3C_6H_4$	CH_3	H	$C_{14}H_{12}N_4O$	201-204.5	EtOH	C, H, N
33	*p*-$CH_3C_6H_4$	CH_3	H	$C_{14}H_{12}N_4O$	226-227.5	EtOH	C, H, N
34	*o*-(*i*-Pr)C_6H_4	CH_3	H	$C_{16}H_{16}N_4O$	179.5-182.5	EtOH	C, H, N
35	*p*-(*i*-Pr)C_6H_4	CH_3	H	$C_{16}H_{16}N_4O$	177.5-180.5	EtOH-*i*-Pr_2O	C, H, N
36	*o*-$EtOC_6H_4$	CH_3	H	$C_{15}H_{14}N_4O_2$	240.5-243.5	MeOEtOH	C, H, N
37	*m*-$EtOC_6H_4$	CH_3	H	$C_{15}H_{14}N_4O_2$	148[d]	EtOH	C, H, N
38	*p*-$EtOC_6H_4$	CH_3	H	$C_{15}H_{14}N_4O_2$	196-198.5	EtOH	H, N, C[c]
39	*p*-$C_4H_9OC_6H_4$	CH_3	H	$C_{17}H_{19}N_4O_2$	~144[d]	EtOH	C, H, N
40	$C_6H_5(CH_2)_2OC_6H_4$	CH_3	H	$C_{21}H_{18}N_4O_2$	155-159.5	EtOH	C, H, N
41	C_6H_5 C_6H_5 | | —CH—CH$_2$	CH_3	H	$C_{21}H_{18}N_4O$	198.5-204	C_6H_6-P	C, H, N
42	3-Py	CH_3	H	$C_{12}H_9N_5O$	200.5 dec	EtOH	C, H, N
43	C_6H_5	CH_3	Br	$C_{13}H_9BrN_4O$	~195[d]	C_6H_6-P	C, H, Br, N
44	Cyclo-C_6H_{11}	C_2H_5	H	$C_{14}H_{18}N_4O$	147.5-150.5	EtOH	C, H, N
45	*p*-(*i*-Pr)C_6H_4	C_2H_5	H	$C_{17}H_{18}N_4O$	160-163	EtOH	C, H, N
46	*p*-$EtOC_6H_4$	C_2H_5	H	$C_{16}H_{16}N_4O_2$	165.5-167.5	EtOH	C, H, N
47	*p*-$EtOC_6H_4$	$CH_2C_6H_5$	H	$C_{21}H_{18}N_4O_2$	117-121.5	EtOH-Et_2O	C, H, N

[a] P = petr ether. [b] Calcd, 62.67; found, 62.15. [c] Calcd, 63.82; found, 64.35. [d] Büchi apparatus.

Acknowledgment. We thank Dr. G. Rosati, of these Research Laboratories, for the pharmacological screening.

References

(1) M. L. Gujral, P. N. Saxena, and R. S. Tiwari, *Indian Med. Res.*, **43**, 637,(1955).
(2) E. C. Taylor, Jr., *J. Amer. Chem. Soc.*, **74**, 1651 (1952).
(3) J. H. Jones, J. B. Bicking, and E. J. Cragoe, Jr., *J. Med. Chem.*, **10**, 899 (1967).
(4) A. Albert and D. J. Brown, *J. Chem. Soc.*, 74 (1953).
(5) S. Gabriel and A. Sonn, *Chem. Ber.*, **40**, 4850 (1907).
(6) D. Pitrè, S. Boveri, and E. Grabitz, *ibid.*, **99**, 364 (1966).