Motor depression in mice was shown by **9** and **4a** at doses of 17 and 20 mg/kg ip, resp.[12]

The fully aromatic analogs **5**, **9**, and **10** were less interesting in the antiinflammatory assays than the corresponding dihydro derivatives.

Experimental Section

General.—Melting points were detd on a Mel-Temp melting point apparatus and are corrected. Uv spectra were detd in MeOH on a Cary recording spectrophotometer, and ir spectra in KBr with a Model 21 Perkin-Elmer spectrophotometer. Nmr spectra were detd in the indicated solvents on a Varian A-60 spectrometer (Me_4Si). Solns were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.

2-Substituted-4,5-dihydrothieno[3,2-*e*]benzothiazoles (4a–4g). (A) Isolated as Hydrobromides.—Equimolar quants of **2**[7] and appropriate thiourea derivs (thiourea, 1,1-dimethylthiourea, 4-methyl-1-piperazinethiocarboxamide,[3] and thiosemicarbazide) in 3.3 ml of EtOH per mmole of **2** were heated at reflux temp for 16 hr, partially concd, and cooled, whereupon the prods crystd. They were recrystd two times from EtOH prior to anal. Their uv spectra had typical max at 225 (ε 23,000), 240 (13,000), 275 (8300) mμ. Other data are in Table II.

(B) Isolated as Free Bases.—Equimolar quants of **2**, Et_3N, and apprropriate thiourea derivs (1-methylthiourea, 1-allylthiourea, 1-phenylthiourea) in 10 ml of EtOH per mmole of **2** were heated at reflux temp for 5 hr, concd, and treated with H_2O, whereupon the prods pptd. They were recrystd from MeOH or Et_2O–hexane. Their uv spectra had typical max at 228 (ε 42,000), 242 (19,000), 268 (12,000), and 3212 (2900) mμ. Other data are in Table II.

2-Aminothieno[3,2-*e*]benzothiazole (5).—A soln of 2.09 g of **4a** in 10 ml of dioxane was stirred and treated dropwise with 2.27 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 3 ml of dioxane. After 30 min the mixt was filtered and the filtrate was concd. Recrystn of the residual solid (1.45 g) from EtOH (charcoal) gave white crystals: mp 238–241°; uv max 230 (ε 28,000), 290 (11,000), 313 (7400), 323 (7600) mμ. *Anal.* ($C_9H_6N_2S_2$) C, H, N; S: calcd, 31.09; found, 31.57.

2-Amino-5,6-dihydrothieno[2,3-*h*]quinazoline (6).—A mixt of 5.41 g of **3**,[6] 3.34 g of guanidine·HCl, and 200 ml of AcOH was heated on a steam bath for 6 hr, cooled, and the cryst product **6**·HCl (2.46 g) was collected. It was converted by NaOH into the free base: mp 211–214° after recrystn from dioxane; uv max 230 (ε 12,800), 245 (12,800), 265 (6300), 322 (8700), 383 (1500) mμ. *Anal.* ($C_{10}H_9N_3S$) C, H, N, S.

4,5-Dihydrothieno[2,3-*g*]-1,2-benzisoxazole (7).—A mixt of 5.09 g of **3**, 2.9 g of hydroxylamine·HCl, and 200 ml of AcOH was heated on a steam bath for 6 hr, treated with charcoal, filtd, and poured onto 350 g of ice. The resulting mixt gave crystals (2.15 g, 43%), mp 40–41.5°, upon storage at 5°. Low-temp recrystn from hexane gave mp 41–42°; uv max 237 (ε 13,000), 244 (12,500), 289 (9100) mμ. *Anal.* (C_9H_7NOS) C, H, N, S.

4,5-Dihydro-2*H*-thieno[2,3-*g*]indazole (8).—A mixt of 3.60 g of **3**, 2.0 ml of hydrazine hydrate, and 80 ml of EtOH was heated at reflux temp for 3 hr, cooled, and treated gradually with H_2O, whereupon crystals formed (2.87 g, 81%). Recrystn from EtOH gave white plates: mp 166–168°; uv max 222 (ε 13,800), 233 (9300), 240 (6700), 263 (6300) mμ. *Anal.* ($C_9H_8N_2S$) C, H, N, S.

Thieno[2,3-*g*]-1,2-benzisoxazole (9) was prepd by the procedure described for **5**. From 1.5 g of **7** was obtd 1.05 g of crude **9**. Recrystn from 50% aq EtOH, followed by low-temp recrystn from hexane gave a white solid: mp 62–63°; uv max 229 (ε 42,000), 256 (6200), 290 (4000), 302 (7000), 313 (7500) mμ. *Anal.* (C_9H_5NOS) C, H, N, S.

2*H*-Thieno[2,3-*g*]indazole (10) was prepd by the procedure described for **5**. From 180 mg of **8** was obtained 170 mg of crude **10**. Recryst from 50% aq EtOH (charcoal) gave mp 221.5–224.5°; uv max 220 (ε 34,000), 268 (5800), 278 (6600), 288 (5800), 299 (10,300), 312 (13,800) mμ. *Anal.* ($C_9H_6N_2S$) C, H, N, S.

(12) See W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966), for details of this assay.

4-Chloro-6,7-dihydrothianaphthene-5-carboxaldehyde (11).—To an ice-cooled soln of Vilsmeier–Haack reagent, prepd from 6.13 g of $POCl_3$ and 30 ml of DMF, was added a soln of 6.08 g of **1** in 30 ml of DMF. The mixt was heated on a steam bath for 1 hr, cooled, and poured onto 200 g of ice. The resulting mixt was made alk with NaOH and extd with CH_2Cl_2. This ext was washed with satd NaCl, dried, and concd to a syrup which crystd upon trituration with Et_2O. Recrystn from hexane gave 1.3 g (17%) of white prisms, mp 60–61°. That substitution had not occurred in the thiophene ring of **11** was shown by the retention of the 2 and 3 protons in the nmr ($CDCl_3$) at δ 7.3 (d, J = 5.5 Hz) and 7.15 (d, J = 5.5 Hz) ppm. *Anal.* (C_9H_7ClOS) C, H, Cl, S.

4,5-Dihydrothieno[2,3-*c*]acridine·HCl (12).—A mixt of 746 mg of **11**, 744 mg of aniline, and 5 ml of AcOH was heated at reflux temp for 3 hr and then concd.[8] Trituration of the residue with Et_2O gave 734 mg (67%) of yellow solid. Recrystn from $CHCl_3$–hexane gave yellow solid, mp 256–259° dec; uv max 222 (ε 31,000), 252 (16,500), 272 (16,300), 333 (8300), 349 (12,000), 377 12,100) mμ. *Anal.* ($C_{15}H_{11}NS$·HCl) C, H, N, S.

The free base had mp 121–124° after recrystn from CH_2Cl_2–hexane.

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectral data, Drs. A. C. Osterberg and E. N. Greenblatt for *p*-quinone writhing and CNS depressant assays, and Dr. A. E. Sloboda for antiinflammatory assays.

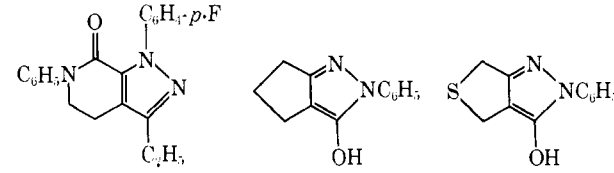
Synthesis and Alkylation of Tetrahydropyrrolo[3,4-*c*]pyrazoles

VICTOR J. BAUER* AND S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

Received May 17, 1971

The pyrazole nucleus is found in a number of antiinflammatory–analgetic drugs such as phenylbutazone,[1] benzydamine,[1] and tetrydamine.[2] Recently, the antiinflammatory activity of the pyrazolopyridone **1** was reported.[3] As an extension of our work on cyclopentapyrazole (**2**)[4] and thienopyrazole (**3**)[5] analogs of the



1 2 3

pyrazole class of antiinflammatory agents, we now describe a brief study of some pyrrolo[3,4-*c*]pyrazoles.

Condensation of ethyl 4-oxo-1-phenyl-3-pyrrolidinecarboxylate (**4**)[6] with appropriate phenylhydrazines gave the hydrazino esters **5a–5e** (solid state ir, 6.0 μ, indicates the enamino ester tautomeric form). Treat-

(1) W. C. Cutting, "Handbook of Pharmacology," 4th ed, Appleton-Century-Crofts, New York, N. Y., 1969, pp 619–626.

(2) G. G. Massaroli, U. S. Patent 3,493,649 (Feb 1970).

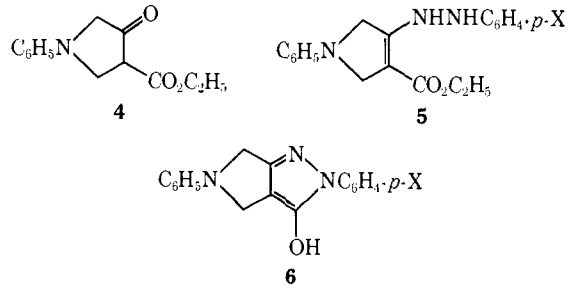
(3) H. M. Blatter, E. Endres, and H. Kulaszenski, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 14; U. S. Patent 3,365,459 (Jan 1968).

(4) R. P. Williams, V. J. Bauer, and S. R. Safir, *J. Med. Chem.*, **13**, 773 (1970).

(5) V. J. Bauer, R. P. Williams, and S. R. Safir, *ibid.*, **14**, 454 (1971).

(6) A. T. de Moulipied, *J. Chem. Soc.*, **87**, 435 (1905).

ment of **5a–5e** with base effected cyclization to the desired pyrrolopyrazolols **6a–6e**. Since solid state ir spectra of **6** fail to exhibit C=O absorption, the com-

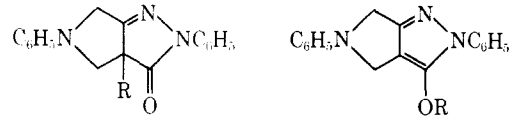


4 **5**

6

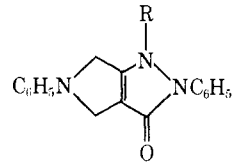
a, X = H; **b**, X = F; **c**, X = Cl; **d**, X = Br; **e**, X = CH_3

pounds exist in the OH form shown. In dil $CHCl_3$ soln, however, **6a** exhibits a C=O band at 5.83 μ, and therefore must assume the unconjugated lactam structure **7a**.



7a, R = H
b, R = $PhCH_2$

8a, R = $PhCH_2$
b, R = $CH_2CH{=}CH_2$



9a, R = $PhCH_2$
b, R = CH_3
c, R = $CH_2CH{=}CH_2$

Reaction of the pyrrolopyrazolol **6a** with alkyl halides under basic conditions proceeded through a tridentate anion to provide, as expected,[4,5] products of C-, N-, and O-alkylation. Thus, $PhCH_2Br$ gave **7b** (ir 5.81 μ), **8a** (ir, no C=O), and **9a** (ir 5.97 μ); MeI gave **9b** (ir 6.00 μ); and allyl bromide gave **8b** (ir, no C=O) and **9c** (ir 5.97 μ).

Oral administration of the pyrrolopyrazoles at 250 mg/kg failed to inhibit significantly the carrageenin-induced rat paw edema[7] when assayed by the method of Winter, *et al.*[8]

Experimental Section[9]

Ethyl 4-(2-*p*-X-Phenylhydrazino)-1-phenyl-3-pyrroline-3-carboxylates (5).—A mixt of 2.24 g (0.01 mole) of ethyl 4-oxo-1-phenyl-3-pyrrolidinecarboxylate,[6] 0.01 mole of an arylhydrazine·HCl, 0.54 g (0.01 mole) of NaOMe, and 50 ml of EtOH was stirred at room temp for 24 hr and filtered. The colorless solid was recrystd; details are included in Table I.

TABLE I

ETHYL 4-(2-*p*-X-PHENYLHYDRAZINO)-1-PHENYL-3-PYRROLINE-3-CARBOXYLATES (5)

X	Mp, °C	Recrystn solv	Formula
H	163–164	EtOH	$C_{19}H_{21}N_3O_2$
F	172–173	EtOH	$C_{19}H_{20}FN_3O_2$
Cl	164–165	EtOH	$C_{19}H_{20}ClN_2O_3$
Br	179–180	MeCN	$C_{19}H_{20}BrN_3O_2$
CH_3	188–189	MeCN	$C_{20}H_{23}N_3O_2$

2-*p*-X-Phenyl-2,4,5,6-tetrahydro-5-phenylpyrrolo[3,4-*c*]-pyrazol-3-ols (6).—A soln of 0.01 mole of an ethyl 4-(2-*p*-X-phenylhydrazino)-1-phenyl-3-pyrroline-3-carboxylate, 0.65 g (0.012 mole) of NaOMe, and 75 ml of EtOH was heated under reflux for 3 hr, filtered, dild with 500 ml of H_2O, treated with charcoal, filtered, and acidified with HCl. The solid which sepd was collected, washed with H_2O, and recrystd; details are included in Table II.

TABLE II

2-*p*-X-PHENYL-2,4,5,6-TETRAHYDRO-5-PHENYLPYRROLO-[3,4-*c*]PYRAZOL-3-OLS (6).

X	Mp, °C dec	Recrystn solv	Formula
H	181–182	MeCN	$C_{17}H_{15}N_3O$
F	189–190	EtOH	$C_{17}H_{14}FN_3O$
Cl	193–194	EtOH	$C_{17}H_{14}ClN_3O$
Br	184–185	EtOH	$C_{17}H_{14}BrN_3O$
CH_3	200–201	EtOH	$C_{18}H_{17}N_3O$

Alkylation of 2,4,5,6-Tetrahydro-2,5-diphenylpyrrolo[3,4-*c*]-pyrazol-3-ol (6a). A. With $PhCH_2Br$.—To a stirred soln of 2.77 g (0.01 mole) of **6a**, 0.60 g (0.011 mole) of NaOMe, and 100 ml of EtOH was added 1.2 ml (0.01 mole) of $PhCH_2Br$. The mixt was stirred at room temp for 24 hr and filtered. The filtrate was concd to an oil which was subjected to preparative tlc.

The band eluted farthest from the origin consisted of 123 mg of brown solid. Recrystn (C_6H_6–hexane) gave colorless crystals, mp 187–188°, ir 5.80 μ, of 3a-benzyl-3a,4,5,6-tetrahydro-2,5-diphenylpyrrolo[3,4-*c*]pyrazol-3(2*H*)-one (**7b**).

A second band consisted of 607 mg of brown solid. Recrystn (MeOH) provided pale yellow crystals, mp 133–134°, ir no C=O below 6.2 μ, of 3-benzyloxy-2,4,5,6-tetrahydro-2,5-diphenylpyrrolo[3,4-*c*]pyrazole (**8a**).

A third band, nearest the origin, consisted of 1.27 g of brown solid. Recrystn (EtOH) gave off-white crystals, mp 201–202°, ir 5.97 μ, of 1-benzyl-1,4,5,6-tetrahydro-2,5-diphenylpyrrolo-[3,4-*c*]pyrazol-3(2*H*)-one (**9a**).

B. With MeI.—To a stirred soln of 2.6 g of **6a**, 0.6 g of NaOMe, and 50 ml of EtOH was added 1.0 ml of MeI. The mixt was stirred at room temp overnight and concd to an oily solid which was subjected to prep tlc. The band nearest the origin consisted of 0.7 g of tan solid, mp 190–195°. Recrystn (EtOH) gave 0.4 g of off-white crystals, mp 221–222°, ir 6.00 μ, of 1,4,5,6-tetrahydro-1-methyl-2,5-diphenylpyrrolo[3,4-*c*]pyrazol-3(2*H*)-one (**9b**).

C. With Allyl Bromide.—To a stirred soln of 2.77 g of **6a**, 0.60 g of NaOMe, and 50 ml of EtOH was added 1.2 ml of allyl bromide. The soln was allowed to stand for 2 days at room temp and concd to an oily solid which was subjected to preparative tlc.

The band farthest from the origin consisted of 25 mg of off-white solid. Recrystn (EtOH) gave colorless crystals, mp 126–127°, ir no C=O below 6.2 μ, of 3-allyloxy-2,4,5,6-tetrahydro-2,5-diphenylpyrrolo[3,4-*c*]pyrazole (**8b**).

The band nearest the origin consisted of 0.5 g of tan solid, mp 189–190°. Recrystn (EtOH) gave off-white crystals, mp 195–196°, ir 5.97 μ, of 1-allyl-1,4,5,6-tetrahydro-2,5-diphenylpyrrolo-[3,4-*c*]pyrazol-3(2*H*)-one (**9c**).

(7) Animal testing was carried out by Dr. A. E. Sloboda of these laboratories.

(8) C. A. Winter, E. A. Risely, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

(9) Melting points were determined in a Hershberg apparatus and are uncorrected. Ir spectra were detd on KBr discs by Mr. W. Fulmor and staff. Microanalyses were performed by Mr. L. M. Brancone and staff. All compds were analyzed for C, H, N, and halogen; found values were within ±0.4% of theor.