Studies on Heterocyclic Systems. 1. 1-Substituted 1,2-Dihydro-2-nitroiminopyridines

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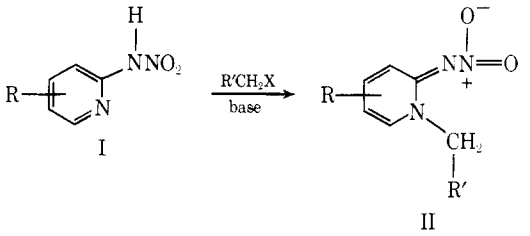
Received February 5, 1971

The alkylation of 2-nitraminopyridine gave products substituted at the ring N. While the nitrimino group was sensitive to aq base it was not affected by basic reagents in nonaq media or by aqueous acid. The *N*-(2-acetophenone) derivative was rearranged in concd H_2SO_4. The title compds were screened for antiinflammatory activity and two of them (**8** and **11**) were found to reduce carrageenin-induced abscess weight.

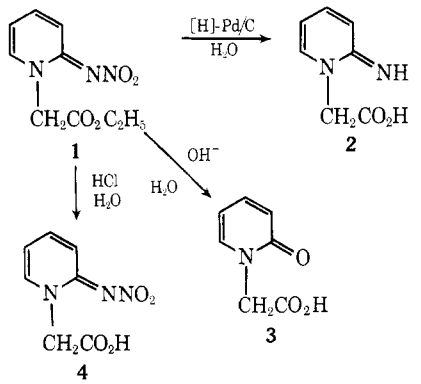
A series of nitriminopyridines of type II were prepared from 2-nitraminopyridines (I) and screened for antiinflammatory activity. Compds of type II should



I II

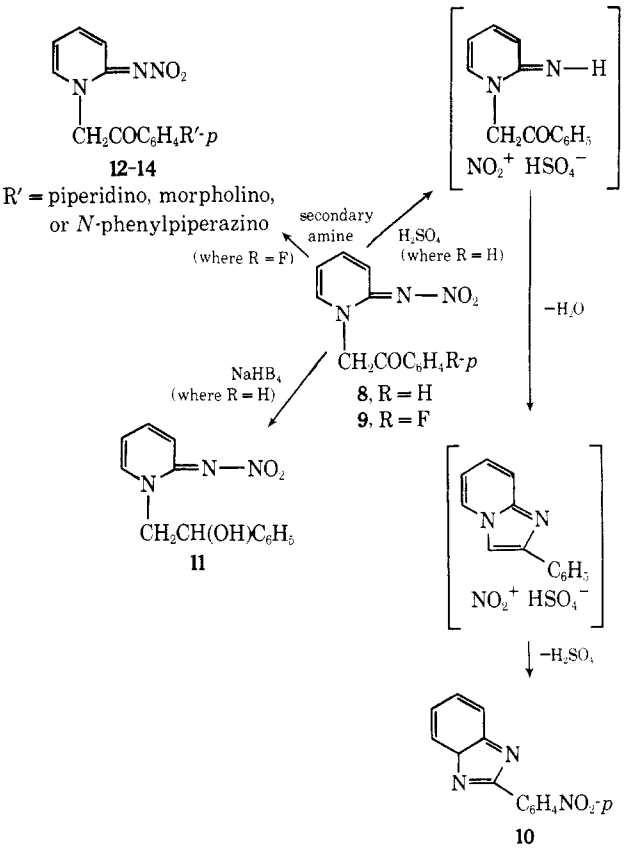
fit the hypothetical antiinflammatory receptor site proposed by Scherrer, *et al.*,[1] and Shen,[2] if the NO_2 group of II can adequately simulate a CO_2H group to satisfy the cationic site.

Chemistry.—2-Nitraminopyridine (I, R = H) was alkylated using ethyl bromoacetate. As alkylation of 2-nitraminopyridines may take place at either the ring N or the exocyclic amino N, depending upon the reactants and conditions,[3] it was necessary to prove the site of alkylation and this was shown in the following way. Reductive cleavage of the N–N bond of the nitro ester so obtained, in aq EtOH, was accompanied by hydrolysis of the ester function to give the known 2-imino-1(2*H*)-pyridineacetic acid (**2**)[4] showing that the starting ester was ring alkylated (**1**).



A comparison of the uv spectrum (MeOH) of this ester (**1**) with the spectra of the other alkylated products of 2-nitraminopyridine (Table IA) showed that the isolated products were substituted at the ring N.[5]

Chichibabin[6] reported that the nitrimino group was labile in aq base, and accordingly, base hydrolysis of the nitrimino ester **1** gave the expected pyridone acid **3**.[7] The nitrimino group was not greatly effected by basic reagents in nonaq media permitting the preparation of amides **5**–**7** from the nitrimino ester **1** and of tertiary amines **12**–**14** from the F compd **9**. The carbonyl



group of the acetophenone derivative **8** was selectively reduced by $NaBH_4$ to give the *dl* alcohol **11**.

The nitrimino group was unaffected by aq HCl as treatment of **1** with 6 *N* HCl resulted only in ester

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(1) R. A. Scherrer, C. V. Winder, and F. W. Short, Abstracts, Ninth Medicinal Chemistry Symposium, Minneapolis, Minn., June, 1964, pp 11a-i; *Annu. Rep. Med. Chem.*, **1964**, 225 (1965).

(2) T. Y. Shen, *Int. Symp. Non-Steroidal Anti-Inflammatory Drugs, Proc.*, **1964**, 13 (1965).

(3) For a review see A. S. Tomcufcik and L. N. Starker, in "Hetrocyclic Compounds: Pyridine and Its Derivatives," Part 3, E. Kingsberg, Ed., Interscience Publishers, New York, N. Y., 1962, p 50.

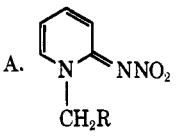
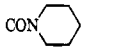
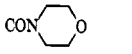
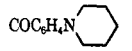
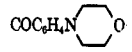
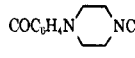
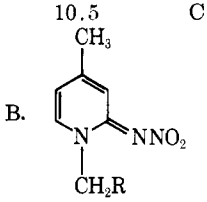
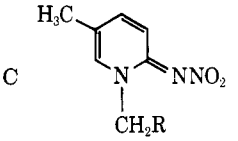
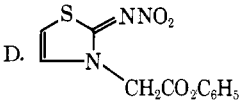
(4) A. E. Chichibabin, *Ber.*, **57B**, 2092 (1924).

(5) The pyridyl portions of 1,2-dihydro-1-alkyl-2-nitriminopyridines (Table I) showed the following characteristic absorption bands. (Note: These were not the only bands in the uv spectra.) With no other substitution λ_{max} was 348, log ϵ 4.25–4.27; with 4-methyl, λ_{max} 344, log ϵ, 4.25–4.28; with 5-methyl, λ_{max} 354, log ϵ, 4.27–4.29.

(6) A. E. Chichibabin, *Ber.*, **58**, 406 (1925); *Chem. Abstr.*, **19**, 1863 (1925).

(7) E. Spath and G. Koller, *Ber.*, **56B**, 880 (1923).

TABLE I

No.	R	Method[a]	Yield,[b] %	Crystn solvent[c]	Mp, °C	Formula[d]
		A. 				
1	$COOC_2H_5$	A	18.2	C	144–147	$C_9H_{11}N_3O_4$
4	COOH	E	60.8	A–B	196–198 dec	$C_7H_7N_3O_4$
5	$CONHNH_2$	G	100.0	A–C	216 dec	$C_7H_9N_5O_3$
6		C	37.8	D	132–133	$C_{12}H_{16}N_4O_3$
7		C	43.9	A–C	186–187	$C_{11}H_{14}N_4O_4$
8	COC_6H_5	B	17.5	B or A–E	191–193	$C_{13}H_{11}N_3O_3$
9	COC_6H_4F-*p*	B	21.8	A–E	216–218	$C_{13}H_{10}FN_3O_3$
11	$CHOHC_6H_5$[e]	D	49.5	A–D	176–180	$C_{13}H_{13}N_3O_3$
12		F	37.8	A–E	197–216 dec	$C_{18}H_{20}N_4O_3$
13		F	36.8	A–E	235–236	$C_{17}H_{18}N_4O_4$[f]
14		F	18.4	A–E	235–237 dec	$C_{23}H_{23}N_3O_3$
15	$COCH_3$	B	4.5	C	144–146 dec	$C_9H_8N_3O_4$
16	$COC_6H_4CF_3$-*m*	B	17.5	A–E	207–208 dec	$C_{14}H_{10}F_3N_3O_3$
17	COC_6H_4Cl-*p*	B	24.6	A–E	209–210 dec	$C_{13}H_{10}ClN_3O_3$
18	$COC_6H_4OCH_3$-*p*	B	26.8	A–E	206–207	$C_{16}H_{13}N_3O_4$
19	$COC_6H_4SO_2CH_3$-*p*	B	36.8	A–E	223–225 dec	$C_{14}H_{13}N_3O_5S$
20	$CH_2C_6H_5$	B	10.5	C	110–112	$C_{13}H_{13}N_3O_2$
		B. 				
21	COC_6H_5	B	38.1	E	119–121	$C_{14}H_{13}N_3O_3$
22	COC_6H_4F	B	29.3	A–C	221–222	$C_{14}H_{12}FN_3O_3$
23	$CH_2C_6H_4$	B	10.7	C	120–122	$C_{14}H_{15}N_3O_3$
		C 				
24	COC_6H_5	B	26.1	A–E	200–203	$C_{14}N_{13}N_3O_3$
25	$COC_6H_4CF_3$-*m*	B	14.7	A–E	198–199	$C_{15}N_{12}F_3N_3O_3$
26	$COC_6N_4SO_2CN_3$-*p*	B	35.8	A–E	212–215 dec	$C_{15}H_{15}N_3O_5S$
		D. 				
27		B	26.1	A–E	211–214 dec	$C_{11}N_9N_3O_3S$

[a] See Experimental Section. [b] Yields are for anal. pure products. [c] A, H_2O; B, MeOH; C, EtOH; D, *i*-PrOH; E, DMF. [d] All compds analyzed for C, H, and N. Analysis are within ± 0.4% of theoretical except where indicated. [e] $[\alpha]^{25}D$ 0 (MeOH). [f] *Anal.* ($C_{17}H_{18}N_4O_4$)H, N, C: Calcd, 59.64; found, 59.21.

cleavage to give the nitrimino acid **4**. 2-[2-(Nitroimino)-1(2*H*)-pyridyl]acetophenone (**8**) suspended in 3 *N* HCl, was unchanged during a 3-hr reflux. This same ketone **8**, however, showed a different behavior in concd H_2SO_4 where it was converted rapidly at 10° to 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (**10**),[8] a reaction involving cyclodehydration and NO_2 migration. The mechanism shown is consistent with the finding of Pentimalli and Bozzini[9] that 2-phenylimidazo[1,2-*a*]-pyridine nitrates at the 4 position of the benzene ring.

The alkylated products as they were obtained from the reaction mixture were reasonably pure and the yields were generally in excess of 50%. Considerable losses were suffered during crystallization of these compds.

Screening Results.—The antiinflammatory model used was the carrageenin abscess test.[10] Female rats (Charles River, Sprague–Dawley C-D) weighing 60–80 g were given the compds at 250 mg/kg po. Phenylbutazone (90 mg/kg po) and aspirin (270 mg/kg po) were used as standards and showed changes in abscess weight of −37 and −27%, resp.

The only alkylated nitriminopyridines to reduce

(8) N. P. BuuHoi and N. D. Xuong, *Bull. Soc. Chim. Fr.*, 1344 (1961).

(9) L. Pentimalli and S. Bozzini, *Boll. Sci. Fac. Chim. Ind. Bologna*, **23**, 181 (1965); *Chem. Abstr.*, **63**, 14848*e* (1965).

(10) S. Goldstein and M. Schnall, *Arch. Int. Pharmacodyn.*, **144**, 269 (1963).

abscess weights more than 20% in this test were 2-[2-(nitroimino)-1(2*H*)-pyridyl]acetophenone (**8**) and its reduction product *dl*-2-(nitroimino)-α-phenyl-1(2*H*)-pyridinethanol (**11**) which caused changes of −31 and −32% resp, in abscess wt. Removal of the O from the benzylic position (**20**) resulted in loss of activity. Acetophenones with substituents on the benzene and pyridine rings all showed changes in abscess wt of less than −20%.

Experimental Section

A.—2-Nitraminopyridine (122 g, 0.87 mole) was added to NaOEt [from Na (20 g, 0.87 g-atom) in EtOH (2 l.)], and the mixt was heated under reflux for 2 hr. Ethyl bromoacetate (145 g, 0.87 mole) was added dropwise over a period of 30 min and the mixt was heated for an addnl 5 hr. The mixt was cooled and the liquor was decanted. The residue was stirred with H_2O (2 l.), and the solid was filtered off to give 118 g (59.8%) yield of crude ethyl 2-nitroimino-1(2*H*)-pyridylacetate (**1**), which was purified by crystn.

B.—The alkyl halide (0.1 mole) was added to a mixt of the nitramino compd (0.1 mole) and Et_3N (0.2 mole) in refluxing EtOH (200 ml). The mixt was heated under reflux for 3 hr, cooled, and filtered. The filter cake was washed with EtOH and purified by crystn.

C.—The ester **1** (11.25 g, 0.05 mole) and the appropriate secondary amine (50 ml) were heated under reflux for 1.5 hr. The excess amine was removed by evapn *in vacuo*. The residue was triturated with C_6H_6, and the resulting solid was filtered off and purified by crystn.

D.—$NaBH_4$ (1.5 g, 0.04 mole) was added in 2 portions, 5 min apart, to **8** (5.4 g, 0.02 mole) in MeOH (100 ml). The mixt was stirred for an addnl 15 min, and the solvent was removed by evapn *in vacuo*. The residue was triturated with H_2O, filtered, and crystn.

E.—A mixt of the ester **1** (10 g) and 6 *N* HCl (100 ml) was heated on a steam bath for 10 min. The resulting mixt was concd to 0.25 vol under reduced pressure, cooled, and filtered. The product was purified by crystn.

F.—This is a modification of the procedure employed by Bader, *et al.*,[11] for the prep of 4-piperidinoacetophenone. The only differences are the use of 3 times their reported vol of DMSO and a heating time of only 90 min.

G.—The ester **1** (11.3 g, 0.01 mole), 95+% H_2NNH_2 (1.7 g), and anhyd EtOH were heated under reflux for 6 hr. The mixt was cooled, and the resulting hydrazide **5** was filtered off and purified by crystn.

Rearrangement of 2-[2-(Nitroimino)-1(2*H*)-pyridyl]acetophenone (8) in H_2SO_4.—Concd H_2SO_4 was cooled to −15° in a Dry Ice-*i*-PrOH bath and **8** (10 g) was added over a period of 1 min during which time the temp rose to 0° then quickly dropped to −15°. The cooling bath was removed and the temp was allowed to rise to +15°. The mixt was poured onto ice, the resulting solid was filtered off and washed with H_2O and crystd (DMF) giving 3.74 g (38.1%) of yellow material, mp 265–267° (lit. 272°).[8] This material was identical (mmp undepressed, and the ir spectra were superimposible) with a sample of 2-(4-nitrophenyl)imidazo[1,2-*a*]pyridine (**10**) prepd according to Buu-Hoi and Xuong.[8] *Anal.* ($C_{13}H_9N_3O_2$) H, N; C: calcd, 65.27; found, 64.40.

Base Hydrolysis of Ethyl 2-(Nitroimino)-1(2*H*)-pyridylacetate (1).—NaOH (2 *N*, 100 ml) was added to the ester (**1**) (11.3 g, 0.05 mole) in EtOH (100 ml). The mixt was heated under reflux for 2 hr. The EtOH was removed by evapn *in vacuo*. The residue was triturated with H_2O and extd with C_6H_6. The aq phase was chilled and made acid to pH 2 with HCl. A solid formed which was filtered off and crystd (*i*-PrOH) to give 4.52 g (53% yield) of 2-pyridone-1(2*H*)-acetic acid (**3**), mp 225–228° (lit. 222°).[7] *Anal.* ($C_7H_7NO_3$) C, H, N.

Catalytic Reduction of the Nitrimino Ester (1).—The ester **1** in 80% EtOH (250 ml) was shaken under 3.1 kg of H_2/cm^2 using 5% Pd/C catalyst (1.5 g). When uptake stopped, the mixt was filtered through a celite pad and the solvent was removed from the filtrate. The residue (6.0 g) crystd (*i*-PrOH-H_2O) as white needles, mp 249–251° (lit. 248–250).[5] This material was identical (mmp undepressed, and the ir spectra were superimposible) with a sample of 2-imino-1(2*H*)pyridineacetic acid (**2**) prepd by the method of Chichibabin.[4] *Anal.* (C_7H_8N) C, H, N.

Acknowledgment.—The authors wish to thank Mr. Frank P. Palopoli for his help and encouragement.

(11) H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

Notes

Antibacterial Nitrofuran Derivatives. 4. 5-Nitro-2-furaldehyde Hydrazoniumacethydrazones

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Received March 27, 1971

We have recently described the synthesis of a series of 5-nitro-2-furaldehyde aminoacethydrazones[1-3] with antibacterial activity. In this paper we have reported a new series of 5-nitro-2-furaldehyde hydrazoniumacethydrazones 4.

Chemistry.—Compds **4** were synthesized by the route outlined in Scheme I. In several cases compds **2** and **3** could not be isolated because of their deliquescence. The structure of these compds was deduced by the following observations.

The structure $\overset{\frown}{N}HCH_2COOC_2H_5$ was excluded because it was not possible to obtain a base by making **2** alkaline. Treatment of **2** with Ag_2O or a strong anionic-exchange resin gave a compd with neither Br^- nor $C_2H_5O^-$ identified as betaine **6**. The structure of **6** was proved by subjecting the products to reductive cleavage with 10% Pd/C, whereupon NH_3 and the corresponding amino acids **7** where obtained. Similar results were obtained by Pollak, *et al.*[4]

By reaction of 1,1-disubstituted hydrazines (**1**) with bromoacetic acid we obtained the double salts **5**. These products by reductive cleavage of N–N bonds with 10% Pd/C yielded **7**, NH_3, and the corresponding secondary amines.

By passing **5** over a strong cationic exchanger and eluting with NH_4OH we obtained **6** and the corresponding products **1**.

(1) E. Massarani, D. Nardi, A. Tajana, and L. Degen, *J. Med. Chem.*, **14**, 633 (1971).

(2) D. Nardi, E. Massarani, S. Rossi, A. Tajana, and L. Degen, *ibid.*, **14**, 635 (1971).

(3) L. Degen, M. Salvaterra, S. Vella, D. Nardi, and E. Massarani, *Chemotherapy*, in press.

(4) G. Pollak, H. Yellin, and A. Carmi, *J. Med. Chem.*, **7**, 220 (1964).