Analogs of the Anorexic Mazindol

T. L. LEMKE ˣ, L. A. CATES, M. STEENBERG, and Y. M. CHO

Abstract □ Mazindol, 5-(*p*-chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol, has been shown to be an effective anorexic. To explore the structure–activity relationships, several 1-ethyl-3-substituted-4-aryl-4-hydroxyindeno[1,2-*c*]pyrazoles were prepared and subjected to various animal screens. The 1-ethyl-3-*tert*-butyl-4-aryl-4-hydroxyindeno[1,2-*c*]pyrazoles are capable of significantly depressing forced and spontaneous motor activity in mice but have low LD_{50}'s. Two of these compounds were tested in an Ehrlich ascites tumor screen. The 1-ethyl-3-phenyl-4-aryl-4-hydroxyindeno-[1,2-*c*]pyrazoles depressed forced and spontaneous motor activity at low doses and were relatively nontoxic.

Keyphrases □ Mazindol analogs—synthesis, effect on forced and spontaneous motor activity, mice □ Indeno[1,2-*c*]pyrazoles, 1-ethyl-3-substituted-4-aryl-4-hydroxy (mazindol analogs)—synthesis, effect on forced and spontaneous motor activity, mice

Recently, a new, chemically unique anorexic was introduced for use as an adjunct in the treatment of obesity. Mazindol (I) is a derivative of the imidazo[2,1-*a*]isoindole nucleus. Not only does this nucleus represent a new basic structure with anorexic activity, but the site of action of mazindol is reportedly different from that of previously used agents (1). This drug, in addition to suppressing appetite, has been reported to cause a mild central nervous system (CNS) stimulation in both laboratory animals and humans (2–4).

The relationship between this unique structure and the anorexic effect apparently has not been explored. Because of an interest in novel tricyclic nuclei, an investigation of the indeno[1,2-*c*]pyrazoles, which have structural features in common with the imidazo[2,1-*a*]isoindole nucleus, was undertaken. The synthesis and initial biological screening of these analogs (II) of mazindol are now reported[1].

EXPERIMENTAL[2]

Chemistry—The indeno[1,2-*c*]pyrazol-4-ones were prepared by the procedure of Braun and Mosher (5) as shown in Scheme I. Grignard addition of arylmagnesium bromides to the 1-ethylindeno[1,2-*c*]pyrazol-4-ones (V) gave the appropriate tertiary alcohols (II*a*–II*f*).

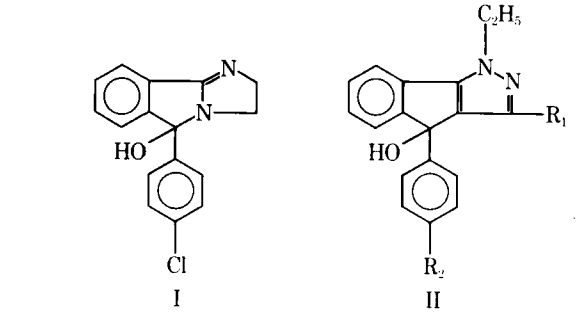
*1-Ethyl-3-*tert*-butylindeno[1,2-c]pyrazole-4(1*H*)-one (V)*—A 9.7-g (0.043-mole) sample of IV (R_1 = *tert*-butyl) (5) was added to 3 liters of 10% sodium hydroxide and heated to boiling. The solution was filtered and cooled, and the resulting solid was collected and dried at 70°, mp > 300°. The solid was added to a solution of 20.0 g (0.18 mole) of ethyl bromide and 150 ml of 100% ethanol and heated at reflux for 16 hr. The solution was cooled to give 9.9 g of material which, after recrystallization from 95% ethanol, gave 7.7 g of product, mp 115–117°; NMR ($CDCl_3$): δ 1.47 (9H, s), 1.63 (3H, t, J = 7 Hz), 4.3 (2H, q, J = 7 Hz), and 7.0–7.5 (4H, m).

Anal.—Calc. for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.63; H, 7.24; N, 10.93.

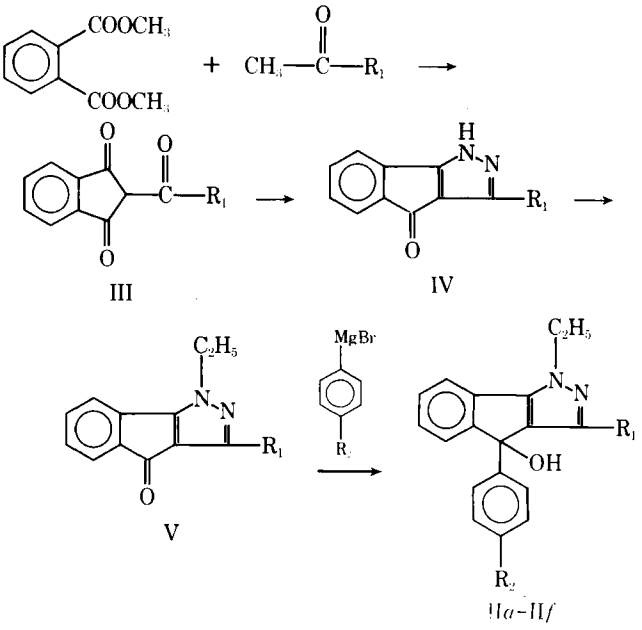
*1-Ethyl-3,4-diphenyl-4-hydroxyindeno[1,2-c]pyrazole (II*a*)*—To 0.96 g (0.04 g-atom) of magnesium in 40 ml of previously distilled tetrahydrofuran was added dropwise 6.28 g (0.04 mole) of bromobenzene in 140 ml of tetrahydrofuran. The reaction was initiated by heating at 70° and stirring under a nitrogen atmosphere. Once the reaction started, addition was at such a rate so as to maintain a gentle reflux. To the Grignard product was added 5.48 g (0.02 mole) of IV (R_1 = C_6H_5) (1) in 80 ml of tetrahydrofuran. The addition took 1.5 hr and was followed by 2 hr of reflux, entirely under a nitrogen atmosphere.

The solvent was removed by distillation, and the residue was added to 200 ml of ice water and allowed to stand overnight. The solid was collected by filtration, dried, and chromatographed on 600 g of silica gel, using methylene chloride as the eluting solvent. The solid coming off the column was recrystallized with ethyl acetate to yield 4.3 g (61%), mp 217–218.5°; NMR ($CDCl_3$–dimethyl sulfoxide-d_6): δ 1.60 (3H, t, J = 7 Hz), 3.07 (1H, b, OH), 4.42 (2H, q, J = 7 Hz), and 6.9–7.8 (14H, m).

Anal.—Calc. for $C_{24}H_{20}N_2O$: C, 81.78; H, 5.72; N, 7.95. Found: C, 81.62; H, 5.76; N, 7.95.



I II



Scheme I

[1] Since this manuscript was submitted, several reports on the chemistry and structure–activity relationship have appeared: P. Aeberli, P. Eden, J. H. Gogerty, W. J. Houlihan, and C. Penberthy, *J. Med. Chem.*, **18**, 177(1975); *ibid.*, **18**, 182(1975); and S. Barcza and W. J. Houlihan, *J. Pharm. Sci.*, **64**, 829(1975).

[2] Melting points were determined with a Thomas-Hoover Unimelt melting-point apparatus and are uncorrected. Chromatography was done on Brinkmann silica gel 60, particle size 0.063–0.2 mm. All products were submitted for NMR analysis on a Varian Associates T-60 or EM-360 and for IR analysis on a Perkin-Elmer 700 spectrophotometer and were consistent with proposed structures. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

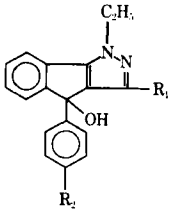


Table I—Acute LD_{50}[a], ED_{50}[b], and Safety Indexes of Mazindol Analogs in Mice

Compound	R_1	R_2	LD_{50}, mg/kg ip	ED_{50}, mg/kg ip	Safety Index, LD_{50}/ED_{50}
IIa	C_6H_5	H	>1000	115	>8.7
IIb	C_6H_5	Cl	>1000	90	>11.1
IIc	C_6H_5	CH_3	>1000	112.0	>8.9
IId	$C(CH_3)_3$	H	172.6	54	3.2
IIe	$C(CH_3)_3$	Cl	43.3	16.8	2.6
IIf	$C(CH_3)_3$	CH_3	485.0	42.5	11.4

[a] The 72-hr LD_{50}. [b] Calculated from Table IV.

1-Ethyl-3-phenyl-4-(p-chlorophenyl)-4-hydroxyindeno[1,2-c]-pyrazole (IIb)—When the same procedure and molar quantities were used as for IIa, 4 g of product was recovered. The solid was chromatographed using chloroform as the eluting solvent to remove the impurity and 5% methanol–chloroform to remove the product. Recrystallization of the product from isopropyl alcohol gave 2.5 g (IIb), mp 230–233°; NMR (dimethyl sulfoxide-d_6): δ 1.57 (3H, t, J = 7 Hz), 4.5 (2H, q, J = 7 Hz), 6.57 (1H, s, OH), and 7.2–8.0 (13H, m).

Anal.—Calc. for $C_{24}H_{19}ClN_2O$: C, 74.51; H, 4.95; Cl, 9.15; N, 7.24. Found: C, 74.36; H, 5.02; Cl, 9.26; N, 7.15.

1-Ethyl-3-phenyl-4-(p-tolyl)-4- hydroxyindeno[1,2-c]pyrazole (IIc)—When the same procedure and molar quantities were used as for IIa, 6.0 g of material was isolated. This material was chromatographed using methylene chloride as the eluting solvent. The product was recrystallized from ethyl acetate to give 4.0 g (IIc), mp 220.5–222.5°; NMR ($CDCl_3$): δ 1.85 (3H, t, J = 7 Hz), 2.22 (3H, s), 3.3 (1H, b, OH), 4.18 (2H, q, J = 7 Hz), and 6.8–7.8 (13H, m).

Anal.—Calc. for $C_{25}H_{22}N_2O$: C, 81.93; H, 6.05; N, 7.65. Found: C, 81.90; H, 6.08; N, 7.63.

1-Ethyl-3-tert-butyl-4-phenyl-4-hydroxyindeno[1,2-c]pyrazole (IId)—The same procedure and molar quantities were used as for IIa, and the concentrated reaction mixture was added to ice water and extracted with ether. The combined ether extract was dried over anhydrous magnesium sulfate. Removal of the solvent followed by chromatography on 600 g of silica gel, using 5% methanol–chloroform as the eluting solvent, resulted in recovery of the product. This product was recrystallized from cyclohexane, mp 142–144°; NMR ($CDCl_3$): δ 1.1 (9H, s), 1.53 (3H, t, J = 7 Hz), 2.43 (1H, b, OH), 4.37 (2H, q, J = 7 Hz), and 7.0–7.5 (9H, m).

Anal.—Calc. for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found: C, 79.41; H, 7.29; N, 8.37.

1-Ethyl-3-tert-butyl-4-(p-chlorophenyl)-4-hydroxyindeno[1,2-c]pyrazole (IIe)—When the same procedure and molar quantities were used as for IIa and the ether extraction was performed as for IId, a solid was recovered. This solid was chromatographed using chloroform as the eluting solvent. Recrystallization from cyclohexane gave 3.1 g of IIe, mp 143–148°; NMR ($CDCl_3$): δ 1.07 (9H,s), 1.47 (3H, t, J = 7 Hz), 3.12 (1H, s, OH), 4.27 (2H, q, J = 7 Hz), and 6.9–7.4 (8H, m).

Table II—Survival Study of Swiss Mice Bearing the Ehrlich Ascites Tumor[a]

Group[b]	Drug	Dose, mg/kg × days	Survival Time, days ± SE	Number of Survivors at 60 days
1	IIe	10 × 9	13.6 ± 1.4	0
2	IId	40 × 9	24.0 ± 9.97	1
3	Control	None	14.8 ± 1.6	0

[a] *Cancer Chemother. Rep.*, 3(2) (1972). [b] Five mice per group.

Table III—Effects of Derivatives of Mazindol on Forced Motor Activity in Mice

Compound	Dose, mg/kg	Third Trial, sec ± SE	Fourth Trial, sec ± SE	Percent of Control
IIa	75	201.6 ± 18.4	156.5 ± 22.4	77.6
	100	218.2 ± 13.5	109.9[a] ± 24.3	50.4
	150	203.1 ± 5.7	169.8 ± 23.8	83.6
IIb	50	200.0 ± 25.3	189.0 ± 19.9	94.5
	100	162.2 ± 20.9	139.3 ± 30.5	85.9
	200	203.5 ± 18.7	174.0 ± 12.1	85.5
IIc	75	184.2 ± 18.5	117.3[a] ± 22.2	63.7
	100	164.1 ± 13.7	108.0[a] ± 17.2	65.8
	150	203.2 ± 22.1	122.3[a] ± 21.4	60.2
IId	25	221.1 ± 7.5	199.5 ± 21.2	90.2
	50	259.0 ± 15.2	225.8 ± 14.6	87.2
	100	196.5 ± 6.9	104.5[a] ± 33.3	53.2
IIe	10	223.3 ± 22.0	225.2 ± 18.0	100.9
	14	226.1 ± 26.9	124.0[a] ± 23.2	54.8
	20	187.8 ± 1.5	67.3[a] ± 25.2	35.8
IIf	12.5	180.4 ± 27.1	163.3 ± 25.9	90.5
	25	166.2 ± 24.1	115.1 ± 22.2	69.3
	50	192.7 ± 15.2	107.1[a] ± 20.7	55.6

[a] $p < 0.05$.

Anal.—Calc. for $C_{22}H_{23}ClN_2O$: C, 72.02; H, 6.32; Cl, 9.66; N, 7.64. Found: C, 72.17; H, 6.34; Cl, 9.76; N, 7.57.

1-Ethyl-3-tert-butyl-4-(p-tolyl)-4-hydroxyindeno[1,2-c]pyrazole (IIf)—When the same procedure and molar quantities were used as for IIa and the ether extraction was performed as for IId, a solid was recovered. This solid was chromatographed using methylene chloride as eluting solvent to give 4.0 g of product. Recrystallization from cyclohexane gave 3.3 g of IIf, mp 153–156°; NMR ($CDCl_3$): δ 1.10 (9H, s), 1.55 (3H, t, J = 7 Hz), 2.28 (3H, s), 4.33 (2H, q, J = 7 Hz), and 6.9–7.4 (8H, m).

Anal.—Calc. for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 8.09. Found: C, 79.68; H, 7.59; N, 8.09.

Pharmacology—Ascites survival studies were performed on male Swiss albino mice, which were implanted intraperitoneally with 4×10^6 Ehrlich ascites cells. Drug treatment was started 24 hr after implantation and injections were given intraperitoneally once daily for 9 days. Drugs were suspended in 0.5% carboxymethylcellulose–saline.

Male Swiss-Webster mice[3], 20–25 g, were used for forced and spontaneous motor activity tests after being acclimated to laboratory conditions for 3–4 days. Each dose was usually tested in six mice, which were permitted food and water *ad libitum*. The six compounds were suspended in 5% polysorbate 80–95% isotonic saline and administered in doses of 10 ml/kg ip. The injection time was 15 sec. The results that differed from control values at the $p < 0.05$ level (Student t-test) were considered statistically significant.

Method—The acute 72-hr intraperitoneal lethal dose effects were determined in mice using three dose levels, and the LD_{50} was estimated using the method of Litchfield and Wilcoxon (6).

Forced and Spontaneous Motor Activity—The effects of the compounds on forced motor activity of mice were studied using the rotarod. The wood rod rotated at 4 rpm for the first 30 sec, at 6 rpm during the next 30 sec, and at progressively increasing speeds thereafter at 30-sec intervals (maximum 50 rpm) until the mouse fell off. Six animals were tested simultaneously and were given four trials with two spaced 4–6 hr apart on each of 2 consecutive days. The fourth trial was preceded by an interval of 50 min for the administration of vehicle or one selected dose of the experimental compounds. The drug or placebo effect for each animal was computed on a ratio of performance time on the fourth trial divided by performance time on the third trial.

The effects of the compounds on the spontaneous motor activity in mice were measured in three photocell cages[4]. Two animals treated with identical doses of the same compound were placed in each photocell cage 10 min after the initiation of the rotarod test, and a 15-min count was initiated 5 min after the animals were placed in the cages. To negate the differences in sensitivity among

[3] Texas Inbred, Houston, Tex.
[4] Actophotometer, Woodward Research Corp.

Table IV—Effects of Derivatives of Mazindol on Spontaneous Motor Activity in Mice

Compound	Dose, mg/kg	Control ± SE	Drug ± SE	Percent of Control
IIa	75	1199.7 ± 215.7	874.0 ± 79.9	72.9
	100	1199.7 ± 215.7	497.3[a] ± 64.3	41.5
	150	1338.7 ± 46.2	733.0 ± 138.8	54.8
IIb	50	1338.7 ± 46.2	851.3 ± 155.4	63.6
	100	1422.3 ± 89.4	591.7[a] ± 120.5	41.6
	200	1422.3 ± 89.4	743.0[a] ± 56.0	52.2
IIc	75	1214.8 ± 95.8	842.3 ± 174.2	69.3
	100	1214.8 ± 95.8	702.7 ± 286.0	57.8
	150	1249.7 ± 195.1	471.3[a] ± 86.4	42.7
IId	25	860.0 ± 44.1	490.0[a] ± 98.1	57.0
	50	860.0 ± 44.1	437.0[a] ± 65.2	50.8
	100	1201.7 ± 45.9	314.0[a] ± 166.1	26.1
IIe	10	1250.8 ± 180.3	1145.7 ± 92.1	91.6
	14	1201.7 ± 45.9	984.7 ± 124.3	81.9
	20	1250.8 ± 180.3	272.0[a] ± 92.9	21.7
IIf	12.5	938.7 ± 35.6	797.7 ± 27.7	85.0
	25	938.7 ± 35.6	694.3 ± 135.4	74.0
	50	1249.7 ± 195.1	534.0[a] ± 86.4	42.7

[a] $p < 0.05$.

units, each dose was tested in a factorial design in each of the three activity cages. Control animals were tested simultaneously at the same time intervals after administration of an equal volume of vehicle, and the ED_{50} of each compound (defined as the dose that decreased the level of performance to 50% of the control scores) was calculated (6).

The percent of control activity (spontaneous and forced motor activity) at each dose level of the compounds used was plotted in an attempt to evaluate the possible types of activity of each compound.

RESULTS AND DISCUSSION

The products synthesized and investigated are shown in Table I along with their LD_{50}, ED_{50}, and safety index values. Derivatives

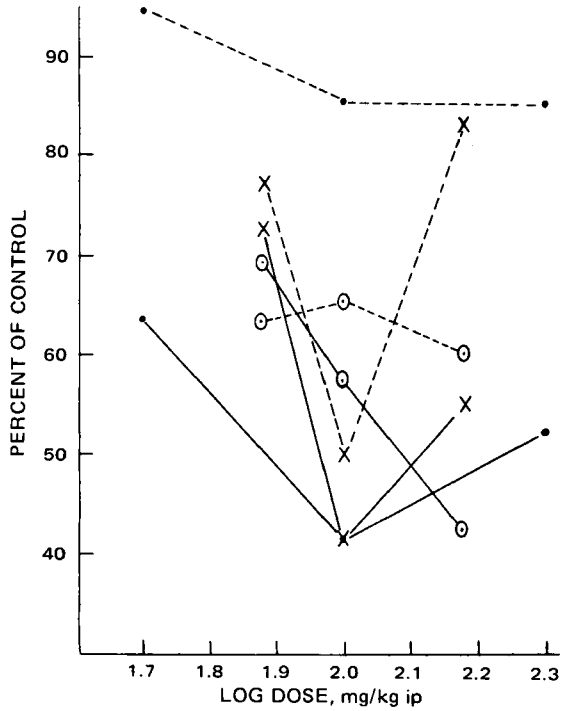


Figure 1—*Decrease in forced and spontaneous motor activity in mice with 1-ethyl-3-phenyl-4-aryl-4-hydroxyindeno[1,2-c]pyrazoles. Key: ——, spontaneous motor activity; - - -, forced motor activity;* ×, *IIa;* ●, *IIb; and* ⊙, *IIc.*

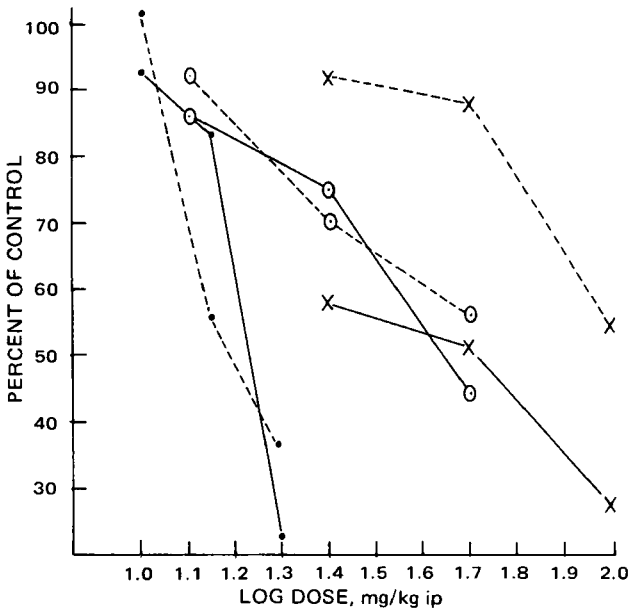


Figure 2—*Decrease in forced and spontaneous motor activity in mice with 1-ethyl-3-*tert*-butyl-4-aryl-4-hydroxyindeno[1,2-c]pyrazoles. Key: ——, spontaneous motor activity; - - -, forced motor activity;* ×, *IId;* ●, *IIe; and* ⊙, *IIf.*

of 1-ethyl-3-phenyl-4-aryl-4-hydroxyindeno[1,2-c]pyrazoles (IIa–IIc) are relatively nontoxic, while the compounds in which a tertiary butyl group has been substituted for the 3-phenyl group are toxic in mice. All compounds, with the exception of IIe, are less toxic than mazindol (LD_{50} 106 mg/kg po).

For all compounds, death was a result of respiratory stimulation and clonic convulsions. Due to a strong interest in potential anticancer agents and, especially, agents possessing the hydrazino moiety (7) such as that found in the pyrazole ring, several of the more toxic agents were submitted to an Ehrlich ascites tumor screen. The results of this preliminary evaluation are shown in Table II.

The compounds were next tested in mice for their effects on forced and spontaneous motor activity, and the results are presented in Tables III and IV, respectively, and in Figs. 1 and 2. Gogerty *et al.* (3) reported that mazindol produced moderate to marked CNS stimulation, appetite suppression, and antidepressant activity in both mice and rats. In studies with the derivatives of mazindol, just the opposite effects were noted, with impressive decreases in spontaneous and forced motor activity. The 1-ethyl-3-*tert*-butyl-4-aryl-4-hydroxyindeno[1,2-*c*]pyrazoles (II*d* and II*e*) were the most potent compounds in reducing both forced and spontaneous motor activity. However, these agents were the more toxic derivatives and for IIe the highest dose used was about 50% of the LD_{50}; the effects may, therefore, be due to a toxic effect. The 1-ethyl-3-phenyl-4-aryl-4-hydroxyindeno[1,2-*c*]pyrazoles (II*a*–IIc) showed a slight decrease in spontaneous and forced motor activity. In two cases (II*a* and II*b*), this decrease was followed by an upward trend in motor activity at higher doses. Perhaps this effect would show an increase at higher doses but the studies were not carried that far.

The antidepressant drugs like imipramine and desipramine when administered in doses of 40 and 60 mg/kg ip to untreated mice, led to ptosis, a decrease in body temperature, and a decrease in both forced and spontaneous motor activity. It is only possible to discover their antidepressant effects by doing a more detailed study of each compound using a battery of tests, including the effects of each compound in reversing the effect of reserpine in mice and rats.

REFERENCES

(1) "Sanorex (Mazindol) A Monograph," Sandoz Pharmaceuticals, East Hanover, N.J., 1973.

(2) R. E. Bagdon, H. A. Hartman, and R. J. vanRyzin, *Fed.*

Proc., **27**, 598(1968).
(3) J. A. Gogerty, W. Houlihan, M. Galen, P. Eden, and C. Penberthy, *ibid.*, **27**, 501(1968).
(4) A. J. Hadler, *J. Clin. Pharmacol.*, **12**, 453(1972).
(5) R. A. Braun and W. A. Mosher, *J. Org. Chem.*, **24**, 648(1959).
(6) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99(1949).
(7) L. A. Cates and T. L. Lemke, *J. Pharm. Sci.*, **63**, 1736(1974).

ACKNOWLEDGMENTS AND ADDRESSES

Received November 25, 1974, from the *Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Houston, Houston, TX 77004*

Accepted for publication January 14, 1975.

The authors acknowledge the assistance of Mr. Walter Hochbrueckner who prepared intermediates needed for this project.

[x] To whom inquiries should be directed.

Effect of Self-Association on Rate of Penicillin G Degradation in Concentrated Aqueous Solutions

JOHN T. H. ONG [*] and HARRY B. KOSTENBAUDER [x]

Abstract □ The apparent rate of degradation of penicillin G potassium micellar solutions of 500,000 units/ml, a concentration commonly encountered in vials reconstituted for storage in the refrigerator, was investigated and compared to that of nonmicellar solutions of 8000 units/ml at 25°, ionic strength of 1.1 *M*, and pH range from 5.0 to 9.5. In the micellar solutions the apparent rate of the H^+-catalyzed degradation was increased twofold but that of water- and OH^--catalyzed hydrolysis was decreased two- to threefold. Consequently, the pH–rate profile of the micellar solutions was shifted to higher pH values and the pH of minimum degradation was found to be at 7.0 compared to 6.5 for the nonmicellar solution of the same ionic strength. Compared at their respective pH–rate profile minima, micellar penicillin G is 2.5 times as stable as the nonmicellar solution under the conditions of constant pH and ionic strength.

Keyphrases □ Penicillin G potassium degradation—concentrated aqueous micellar solutions compared to nonmicellar solutions, pH–rate profiles □ Degradation of penicillin G potassium—concentrated micellar aqueous solutions compared to nonmicellar solutions, pH–rate profiles □ Micellar solutions of penicillin G—degradation compared to nonmicellar solutions, pH–rate profiles

The kinetics of penicillin G degradation in aqueous solution have been studied extensively. The effects of pH, temperature, buffers, ionic strength, metal ions, and model catalysts that simulate penicillinase and other enzymes have been investigated (1–6). The effect of surfactants below and above their critical micelle concentration (CMC) was also studied, with the finding that at pH 6.5 all surfactants studied enhanced the rate of penicillin G degradation (7).

The present study was undertaken to assess the kinetics of penicillin G degradation at concentrations above the CMC, particularly at 500,000 units/ml as encountered in hospital usage, and to obtain a comparison of the pH of minimum degradation for solutions above and below the CMC. Instead of buffer, the pH-stat technique was utilized to maintain a constant pH in these studies. The dilution obtained in all studies was negligible due to the very high concentration of titrant (15 *M* KOH) used.

BACKGROUND

In the earlier studies (1–7), relatively low concentrations of penicillin G were used (8000 units/ml or 0.5% w/v). Literature pertaining to the kinetics of penicillin G degradation at high concentration is limited to observations of the percent degraded after a certain time under specific conditions. Although several results tend to indicate that penicillin G degrades faster at higher concentration, no definitive comparison between the degradation rates at the high and low concentrations can be made because the solutions studied were either unbuffered (8, 9) or inadequately and not proportionally buffered (10, 11). Inadequate buffering of concentrated solutions of penicillin G could give an inordinately large apparent rate of degradation due to a marked pH decrease from the production of large quantities of penicilloic acid.

It has been common practice, particularly in hospitals, to batch-reconstitute buffered penicillin G solutions at a concentration of 500,000 units/ml (30% w/v) and store them frozen until needed. Periodically, the frozen solutions are moved into the refrigerator and kept in a liquid state ready to be diluted with intravenous infusion fluid and administered to patients. According to the manufacturer, sterile solutions in the refrigerator may be kept for 1 week without significant loss of potency. Knowledge of the pH of minimum degradation at this high concentration becomes essential.

The formation of micelles of penicillin G in aqueous solution was first observed by Hauser *et al.* (12). Later studies (13, 14) found the CMC to be relatively high, *i.e.*, 0.25 molal, 130,000 units/ml, or 8.26% (w/v). This value was further confirmed using the data of the NMR (100 MHz) chemical shift of the aromatic protons (15). It was indicated that the number of penicillin G ions that come together to form the aggregates is probably not very large.

In recent years, reactions in micellar systems have been increasingly investigated. Extensive reviews of the kinetic and mechanistic implications of micellar catalysis have been presented (16, 17). From the drug product stability point of view, micellization is important because it can either increase or decrease the stability of a drug, depending on the nature of the micelle and the reaction involved. Thus, catalytic effects of micelles have been observed when both reactants are enriched within the micelles for a bimolecular process. A study (18) of the accelerated fading of cationic triphenylmethane dyes in alkaline solutions of the quaternary surfactant cetyltrimethylammonium bromide has become classic. The micelle itself can serve as a substrate for the reaction, *e.g.*, micellization enhances the rate of H^+-catalyzed hydrolysis of sodium lauryl sulfate by 30-fold over that in a single ion state (19). Conversely,