Some Substituted 5*H*-Indeno[1,2-*d*]pyrimidines (1)

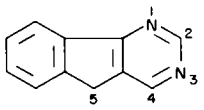
E. Campaigne and H. R. Burton (2)

The Chemistry Laboratories, Indiana University

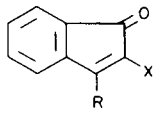
Interest in antimalarial agents has resulted in the reinvestigation of some nitrogen heterocyclic systems which may have antimalarial activity. We recently reported a new synthesis of the indeno[1,2-*d*]pyrimidine ring system (I) (3) which is structurally related to the folic acid antagonist, pyrimethamine, except that it is a tricyclic planar molecule. Modest and coworkers (4) have suggested that such planarity may enhance antimalarial activity in folic acid antagonists.

Up to the present there has been relatively few reports of the syntheses of the 5*H*-indeno[1,2-*d*]pyrimidine ring system (I) (5) and in our present investigation, a study was made on some new approaches for the synthesis of this heterocyclic system I with particular attention to substituents at the 2-, 4-, and 5-position of the ring system. A convenient route for the synthesis of this system was the conversion of the appropriately substituted indanone to its pyrimidine derivative by a series of straightforward reactions. We have reported (6) a synthesis of 2-carboxamido and 2-cyano-5-alkyl or aryl substituted indenones (II) which were found to be useful intermediates in this study. These indenones were catalytically reduced using platinum oxide to form the corresponding indanones III in excellent yield (Table I).

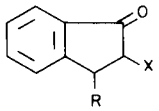
The indanones III, (R = phenyl or *t*-butyl; X = CN or $CONH_2$) reacted readily with ammonia and ammonium nitrate in refluxing ethanol (7,8) or ammonium formate (9) to afford the aminoindene derivatives IV. However, when the R group was ethyl or isopropyl, only the starting materials were recovered from this reaction. The effect of the R group in IV on the stability of the enamines is related to the extent of enolization in III. When the R group is small, the indanone was found to be predominantly in the keto form. However, if the R group was bulky, as phenyl or *t*-butyl there is sufficient steric interaction of the R group and carboxamide or cyano function to cause enolization. These tautomeric forms were readily seen by infrared spectroscopy since the carbonyl band at 1590 cm^{-1} in the infrared spectra of IIIa and IIIb due to carbonyl absorption was absent in IIIc, d and e indicating that the tautomer was predominantly in the enol form. By analogy; one would predict that the nitrogen derivatives of IV, where R is small, would preferentially exist as the less stable imines, and hence might not be isolated. The limitations of these



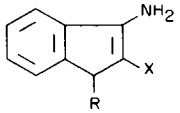
I



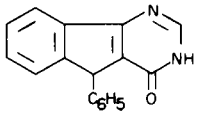
II



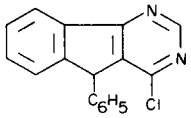
IIIa) R = C_2H_5, X = $CONH_2$
b) R = $CH(CH_3)_2$, X = $CONH_2$
c) R = C_6H_5, X = $CONH_2$
d) R = C_6H_5, X = CN
e) R = $C(CH_3)_3$, X = CN



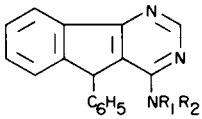
IVa) R = $C(CH_3)_3$, X = CN
b) R = C_6H_5, X = $CONH_2$
c) R = C_6H_5, X = CN



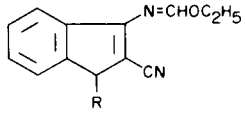
V



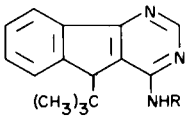
VI



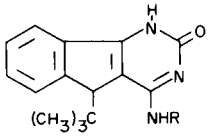
VIIa) R_1 = H, R_2 = $(CH_2)_2N(C_2H_5)_2$
b) R_1 = H, R_2 = $(CH_2)_3N(C_2H_5)_2$
c) R_1 = R_2 = C_2H_5
d) R_1R_2 = $-(CH_2)_5-$
e) R_1 = R_2 = H



VIIIa) R = $C(CH_3)_3$
b) R = C_6H_5



IXa) R = H
b) R = $(CH_2)_2N(C_2H_5)_2$

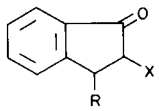


Xa) R = H
b) R = CH_3CO

reactions have limited the diversity of substitution at the 3-position of the 1-aminoindenones and therefore excludes this particular reaction sequence as a general synthetic route in the synthesis of 5-substituted indeno[1,2-*d*]-pyrimidines.

The aminoindene derivatives were found to undergo typical reactions in the formation of the pyrimidine ring

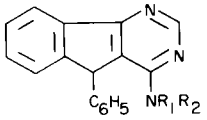
TABLE I
2-Carboxamido(cyano)-3-alkyl(phenyl)indanones (III)



No.	R	X	Yield %	M.P. °C	Anal. Calcd.			Found		
IIIa,	CH_2CH_3	$CONH_2$	34	94-95	$C_{12}H_{13}NO_2$	C, 70.91;	H, 6.45; N, 6.89.	C, 70.69;	H, 6.78;	N, 7.05
IIIb,	$CH(CH_3)_2$	$CONH_2$	74	119-120	$C_{13}H_{15}NO_2$	C, 71.86;	H, 6.96; N, 6.45.	C, 72.22;	H, 7.07;	N, 6.45
IIIc,	C_6H_5	$CONH_2$	82	157-159	$C_{16}H_{13}NO_2$	C, 76.47;	H, 5.22; N, 5.51.	C, 76.62;	H, 5.36;	N, 5.49
IIId,	C_6H_5	CN	83	149-150	$C_{16}H_{11}NO$	C, 82.38;	H, 4.75; N, 6.01.	C, 82.58;	H, 4.80;	N, 6.28
IIIe,	$C(CH_3)_3$	CN	86	117-118 (a)						

(a) M.p. 116-117, Campaigne and Roelofs, *J. Org. Chem.*, 30, 396 (1965).

TABLE II
4-Alkylamino-5-phenyl-5*H*-indeno[1,2-*d*]pyrimidines (VII)



No.	R_1	R_2	Yield %	M.P. °C	Formula	Anal. Calcd.			Found		
VIIa,	H	$CH_2CH_2N(CH_2CH_3)_2$	75	102-103	$C_{23}H_{26}N_4$	C, 77.06;	H, 7.31;	N, 15.63.	C, 77.08;	H, 7.33,	N, 15.56.
VIIb,	H	$(CH_2)_3N(CH_2CH_3)_2$	63	100-101	$C_{24}H_{28}N_4$	C, 77.38;	H, 7.58;	N, 15.04.	C, 77.12;	H, 7.66;	N, 14.81.
VIIc,	CH_2CH_3	CH_2CH_3	66	107-108	$C_{21}H_{21}N_3$	C, 79.96;	H, 6.71;	N, 13.32.	C, 79.92;	H, 6.90;	N, 13.33.
VIId,		$-(CH_2)_5-$	73	150-151	$C_{22}H_{21}N_3$	C, 80.70;	H, 6.47;	N, 12.84.	C, 80.65;	H, 6.73;	N, 12.60.
VIIe	H	H	31	280-282	$C_{17}H_{13}N_3$	C, 78.74;	H, 5.05;	N, 16.21.	C, 78.79;	H, 5.32;	N, 16.00.

system. When 3-amino-2-carboxamido-1-phenylindene (IVb) was refluxed with excess triethyl orthoformate and acetic anhydride, indeno[1,2-*d*]pyrimidine-4-one (V) was isolated in quantitative yield. Treatment of V with phosphorus oxychloride gave the desired 4-chloro-5-phenylindeno[1,2-*d*]pyrimidine (VI) which was found to readily undergo nucleophilic displacement in the presence of aliphatic amines to afford the 4-alkylamino derivatives VII (Table II).

In a similar manner, the β-cyanoenamines (IV) reacted with excess orthoester and acetic anhydride (10) to yield the corresponding intermediate imidates VIII. Subsequent treatment of the crude imidate VIIIa with alcoholic ammonia gave the 4-amino-5-*t*-butylindeno[1,2-*d*]pyrimidine (IXa). If the imidate VIIIa was treated with diethylaminoethylamine, the corresponding 4-diethylaminoethylamino derivative IXb was obtained, *via* a Dimroth rearrangement (11). Fusion of 3-amino-2-cyano-1-*t*-butylindend (IVa) with urea produced 4-amino-5-*t*-butyl-1*H*-indeno[1,2-*d*]pyrimidine-2-one (Xa). However, reaction of IVa with guanidine or thiourea under a variety of conditions (12) resulted in recovery of the starting material. The ability of urea to undergo ring closure may be based on the fact that on heating, it rearranges to the reactive ammonium isocyanate, hence there is no necessity for displacement of the amine nitrogen atom. The stability of enamine IVa toward nucleophilic displacement is shown by its quantitative recovery from boiling water.

It was hoped that compound X could be converted to its 2-chloro derivative by interconversion of the 2-carbonyl group. Compound Xa was found to be inert to nucleo-

philic displacement in the presence of refluxing phosphorus oxychloride. On treatment of Xa with acetic anhydride in pyridine according to the procedure of Baker (13) the corresponding 4-acetylamino derivative Xb was obtained, but we were unable to obtain the desired 2-chloro derivative by the usual treatment.

Some of these compounds were screened for potential antimalarial activity by the Walter Reed Army Institute of Research, using the procedure described by Osdene, *et al.* (14). We are indebted to the W.R.A.I.R. for the results of these tests. None of the compounds submitted (V, VI, VIIa-c, IXa,b) showed significant activity at the 640 mg/kg dose level.

EXPERIMENTAL

Melting points were determined on Mel-Temp apparatus. Infrared spectra were recorded on a Perkin Elmer 137D spectrophotometer. Micro analyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana.

3-Substituted-2-cyano or 2-carboxamido-1-indanones (III).

The indenone II (6) (0.1 mole) and platinum oxide (0.4 g.) were suspended in absolute ethanol (250 ml.) and subjected to hydrogenation (45 p.s.i.) in a Paar hydrogenator at room temperature for 6-8 hours. The catalyst was filtered and the ethanol evaporated under reduced pressure, giving a pale yellow solid or yellow oil, which readily recrystallized from benzene or benzene-petroleum ether (Table I).

Preparation of Aminoindenes. Method A. 3-Amino-2-cyano-1-*t*-butylindene (IVa).

2-Cyano-3-*t*-butyl-1-indanone (IIIe) (2.18 g., 0.01 mole) and ammonium nitrate (1.0 g.) were dissolved in absolute ethanol and the reaction mixture was heated to 85° in an oil bath. Anhydrous ammonia was passed through the refluxing solution for 2.5 days and absolute ethanol was added periodically to maintain the volume of the alcoholic solution. The purple reaction solution was cooled to room temperature and water (25 ml.) was added. After filtration of the crude material, it was crystallized as colorless plates from benzene-petroleum ether (b.p. 30-60°), 1.3 g. (60%), m.p. 119°; ir (potassium bromide), 2.90 and 3.0 (NH_2), 3.09, 3.41 (CH), 4.61 (CN), 6.06 μ (NH_2).

Anal. Calcd. for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.16; H, 7.77; N, 12.93.

3-Amino-2-carboxamido-1-phenylindene (IVb).

Anhydrous ammonia was passed through a refluxing solution of IIIc (4.62 g., 0.02 mole), and ammonium nitrate (2.0 g.) in absolute ethanol (50 ml.) for 2 days, as previously described for IVa. After cooling, the dark blue solution was let stand overnight at room temperature, and the light blue product collected and crystallized from ethanol, yielding 4.00 g. (85%) of IVb as pale blue needles, m.p. 198-200° dec.; ir (potassium bromide), 2.9, 3.02 and 3.12 (NH_2), 6.14 μ (amide).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.84; H, 5.87; N, 10.89.

Method B. 3-Amino-2-cyano-1-*t*-butylindene (IVa).

A solution of IIIe (52.3 g., 0.24 mole) and ammonium formate (32.0 g.) in absolute ethanol (250 ml.) was heated under reflux with stirring for 3 days, concentrated to one-third volume and the product was collected and washed with water giving 40.8 g. (78%) of IVa, m.p. 119°, identical in all respects to that prepared by Method A.

3-Amino-2-carboxamido-1-phenylindene (IVb).

In a similar manner, IIIc (54 g., 0.21 mole) and ammonium formate (36 g., 0.6 mole) in absolute ethanol (440 ml.), worked up as above, yielded 44 g. (82%) of IVb, m.p. 199-200°, identical in all respects to that prepared by Method A.

3-Amino-2-cyano-1-phenylindene (IVc).

2-Cyano-3-phenyl-1-indanone (IIId) (11.1 g., 0.05 mole) and ammonium formate (4.78 g.) in absolute ethanol was treated as above, and the product, crystallized from ethanol, gave 7.1 g. (62%) of pale yellow prisms, m.p. 177°; ir (potassium bromide), 2.87 (NH_2), 3.95 (CN), 6.05 μ (NH_2).

Anal. Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.81; H, 4.97; N, 11.95.

5-Phenyl-3*H*-indeno[1,2-*d*]pyrimidine-4-one (V).

After IVb (2.50 g., 0.01 mole) was heated under reflux with triethyl orthoformate (12.5 ml.) and acetic anhydride for 4 hours and cooled to room temperature, the white crystalline product was collected by filtration and boiled with dimethylformamide, yielding 2.3 g. (88%) of V as colorless prisms, m.p. 338-340° dec.; ir (potassium bromide), 3.56 (CH), 6.1 μ (C=O).

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.48; H, 4.65; N, 10.76. Found: C, 78.68; H, 4.88; N, 11.02.

4-Chloro-5-phenylindeno[1,2-*d*]pyrimidine (VI).

A mixture of V (5.2 g., 0.02 mole) and freshly distilled phosphorus oxychloride (20 ml.) was warmed on a steam bath. After one-half hour, solution had been affected and the reaction mixture was warmed for an additional hour. The excess phosphorus oxychloride was removed under reduced pressure and the residue was decomposed with ice and 20% sodium hydroxide solution. The crystalline material was collected and recrystallized from cyclohexane as colorless needles, 4.2 g. (76%), m.p. 163°.

Anal. Calcd. for $C_{17}H_{11}ClN_2$: C, 73.21; H, 3.89; N, 10.05. Found: C, 73.18; H, 4.04; N, 9.93.

4-β-Diethylaminoethylamino-5-phenylindeno[1,2-*d*]pyrimidine (VIIa).

4-Chloro-5-phenyl-5*H*-indeno[1,2-*d*]pyrimidine (VI) (2.79 g., 0.01 mole) and β-diethylaminoethylamine (2.32 g., 0.02 mole) in absolute ethanol were heated under reflux for 4 hours. The ethanol was removed under a stream of air and the residue was dissolved in boiling aqueous ethanol. After storing in the refrigerator for two weeks, 2.7 g. (75%) of product was collected, which crystallized from cyclohexane as colorless prisms (see Table II).

Compounds VIIb, VIIc, and VIId were prepared in a similar manner, using the appropriate amine, and are reported in Table II.

4-Amino-5-*t*-butylindeno[1,2-*d*]pyrimidine (IXa).

A mixture of triethyl orthoformate (12.3 ml.), acetic annydride (8.6 ml.) and IVa (3.20 g., 0.015 mole) was heated under reflux for 3 hours. After standing overnight, the excess acetic anhydride and orthoester were removed under reduced pressure. The crude imidate VIIIa was poured into an alcoholic ammonia solution (50 ml.) and the solution was stirred for 2 hours at room temperature. The solution was evaporated to dryness under a stream of

air and benzene was added to the viscous oil which soon crystallized. The crystalline product was collected, washed with water, and recrystallized from 50% aqueous ethanol giving 1.15 g. (32%) of pale yellow prisms, m.p. 288-290°; ir (potassium bromide), 2.97 and 3.02 (NH_2), 3.22 (CH), 6.09 μ (NH_2).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.28; H, 7.16; N, 17.56. Found: C, 74.99; H, 7.36; N, 17.58.

Formation of 4-Amino-5-phenylindeno[1,2-*d*]pyrimidine (VIIe).

A mixture of IVc (3.48 g., 0.015 mole), triethyl orthoformate (12.3 ml.) and acetic anhydride (8.6 ml.) was heated under reflux for 4 hours. The excess orthoester and acetic anhydride were removed under reduced pressure leaving a crystalline residue of crude VIIIb. A solution of ethanolic ammonia (50 ml.) was added to the residue and the reaction mixture was allowed to stand at room temperature for 24 hours. The crystalline pyrimidine VIIe was collected and recrystallized from dimethylformamide, 1.2 g. of colorless prisms (31%), m.p. 280-282°; ir (potassium bromide), 3.25 (CH), 6.13 μ (NH_2) (see Table II).

4-(β-Diethylaminoethylamino)-5-*t*-butylindeno[1,2-*d*]pyrimidine (IXb).

Crude imidate VIIIa prepared from 4.3 g. (0.02 mole) of IVa as above, and β-diethylaminoethylamine, (2.36 g., 0.02 mole) in absolute ethanol (40 ml.) were heated under reflux for 18 hours. The ethanol was removed under reduced pressure and a 10% aqueous sodium carbonate solution was added to the viscous oil. Extraction of the aqueous layer with three 20 ml. portions of ether and removal of the ether gave a viscous oil which was dissolved in boiling petroleum ether (b.p. 30-60°), treated with Norit and filtered. Several crystallizations of the product from pentane gave 1.1 g. (17%) of IXb as colorless needles, m.p. 71-72°.

Anal. Calcd. for $C_{21}H_{30}N_4$: C, 74.51; H, 8.93; N, 16.55. Found: C, 74.55; H, 8.93; N, 16.12.

4-Amino-5-*t*-butyl-1*H*-indeno[1,2-*d*]pyrimidine-2-one (Xa).

Urea (4.0 g.) and 4.0 g. (0.019 mole) of IVa were heated at 200-210° for 2 hours at which time a product crystallized from the melt. The crude product (4.3 g.) was found to be insoluble in most organic solvents and in acetic acid. The material was boiled with several portions of dimethylformamide, which on cooling gave 2.0 g. (43%) of pale yellow prisms, m.p. 300°; ir (potassium bromide), 3.03 (NH, OH), 5.8 μ (C=O).

Anal. Calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.71; H, 6.84; N, 16.68.

4-*N*-acetylamino-5-*t*-butylindeno[1,2-*d*]pyrimidine-2-one (Xb).

Warming 3.75 g. (0.014 mole) of Xa on a steam bath with pyridine (20 ml.) and acetic anhydride (6 ml.) for 2 hours, separating the insoluble portion, and pouring the dark green mother liquor into water precipitated the crude *N*-acetyl derivative. Crystallization of the crude material from ethanol gave 2.5 g. (63%) of gray needles, m.p. 292-293° dec.; ir (potassium bromide), 3.18 (NH), 3.37 μ (CH), 6.07 (amide).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.66; H, 6.44; N, 14.13. Found: C, 68.76; H, 6.68; N, 14.23.

REFERENCES

(1) Contribution No. 1793, supported in part by Grant GM-10366 of the National Institutes of Health, to Indiana University. A preliminary report of this work has been presented: E. Campaigne and H. R. Burton, Abstracts of Papers, 151st National Meeting of the American Chemical Society, Pittsburgh, Pa. March 28. 1966.

(2) Postdoctoral Fellow, Indiana University, 1964-1966. Present address: University of Kentucky, Lexington, Kentucky, 40506.

(3) E. Campaigne and W. L. Roelofs, *J. Org. Chem.*, **30**, 396 (1965).

(4a) A. Rosowsky and E. J. Modest, *ibid.*, **31**, 2607 (1966); (b) E. P. Burrows, A. Rosowsky and E. J. Modest, *ibid.*, **32**, 4090 (1967).

(5a) M. Polonovski and D. Liberman, *Bull. Soc. Chim.* (France), 1074 (1947); (b) K. Dziewanski, J. Schoen, S. Ochab, and K. Bagdanowicz, *Rocz, Chem.*, **37**, 561-568 (1963); (c) E. J. Modest, S. Chatterjee and H. Kanzu, *J. Org. Chem.*, **27**, 2708-2709 (1962).

(6) E. Campaigne, G. F. Bulbenko, W. E. Kreighbaum and D. R. Maulding, *ibid.*, **27**, 4428-4432 (1962).

(7) T. H. Conners and W. C. J. Ross, *J. Chem. Soc.*, 2119-2132 (1960).

(8) G. deStevens, *J. Am. Chem. Soc.*, **87**, 6292 (1959).

(9) P. L. Southwick and G. H. Hoffman, *J. Org. Chem.*, **28**, 1332 (1963).

(10) E. C. Taylor and E. E. Garcia, *ibid.*, **29**, 2116 (1964) and references therein.

(11) D. J. Brown, "Heterocyclic Compounds. The Pyrimidines", J. Wiley and Sons, Interscience, New York, N. Y., 1962, pp. 379-380.

(12) G. deStevens, H. Halamandaris, P. Wenk, K. A. Mull and E. Schlitter, *Arch. Biochem. and Biophys.*, **83**, 141 (1959).

(13) B. R. Baker, C. E. Morreal and Beng-Thong Ho, *J. Med. Chem.*, **6**, 658 (1963).

(14) T. S. Osdene, P. B. Russell and L. Rane, *ibid.*, **10**, 431 (1967).

Received March 11, 1970 Bloomington, Indiana, 47401