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Analogs of Tetrahydrofolic Acid. XXIX. Hydrophobic Bonding to Dihydrofolic Reductase. II. On the Mode of Phenyl Binding of 1-aryl-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazines (1,2)

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The inhibition of dihydrofolic reductase by twenty appropriately 1-substituted-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazines were compared in order to shed light on the mode of phenyl binding of 1-aryl-1,2-dihydro-*s*-triazines. When the 1-phenyl group was substituted by a cationic group at the 4-position or an anionic group at either the 3- or 4-position, a large loss in affinity by the enzyme for the resultant inhibitor was noted. This loss in affinity is best explained by the concept that the 1-aryl group complexes with a hydrophobic region on the enzyme and that the hydrophobic region repels any aryl group bearing either a positively or negatively charged group. *p*-Substituents coplanar with the 1-aryl group caused a steric interaction with the enzyme resulting in considerable loss in binding to this enzyme isolated from pigeon liver; this steric effect was considerably less in the *m*-position. Inductive effects of 1-phenyl substituents on a possible charge-transfer complex of the 1-aryl group or on the binding ability of the 4,6-diamino-1,2-dihydro-*s*-triazine ring system could not be correlated with the Hammett sigma-values; therefore these effects were considered to be of minor importance.

That 5-aryl-2,4-diaminopyrimidines and 1-aryl-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazines are excellent inhibitors of dihydrofolic reductase has been known over a decade (3,4). A recent study (5) in this laboratory showed that the phenyl group (I) gave about a 2000-fold increase in binding to dihydrofolic reductase compared to 2,4-diamino-6-methyl pyrimidine or the 1-methyl-1,2-dihydro-2,2-dimethyl-*s*-triazine (II) (Table I), respectively. Since these recent studies also showed that an isoamyl group (III) could give the same order of binding as the aryl group and since the isoamyl group can only bind to the enzyme by a combination of hydrophobic bonding (6) and van der Waals forces, it was proposed that the phenyl group was also complexed to the enzyme by these two forces (5). Additional evidence that these aryl groups complex to dihydrofolic reductase by hydrophobic bonding is presented in this paper.

The following different ways can be envisioned for the mode of complexing of an aryl group of the 1-aryl-dihydrotriazines to dihydrofolic reductase:

(a) a charge-transfer complex (7); (b) an inductive effect of the aryl group on the binding of the 4,6-diamino-*s*-triazine system (8); (c) van der Waals forces (6d); (d) hydrophobic bonding (6).

Furthermore, combinations of these four factors could occur. For example, hydrophobic bonding without van der Waals interactions and *vice versa* is unlikely by the definition that hydrophobic bonding results from the reassociation of water molecules when the hydrocarbon part of an inhibitor or substrate becomes located adjacent to a hydrophobic portion of the enzyme. It is also possible for a combination of hydrophobic bonding and factors (a) and (b) to coexist. At this point the relative energetics of binding by the four classes should be considered since the 1-phenyl-*s*-triazine (I) complexes with dihydrofolic reductase about 2000-fold better than the corresponding 1-methyl-*s*-triazine (II) (5) (Table I), a matter of about 4.5 kcal./mole.

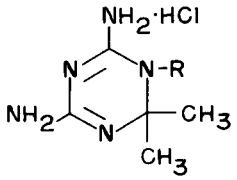
Hydrophobic bonding and van der Waals forces can each contribute about 0.7 kilocal./mole/methylene group (6); thus a phenyl group could be anticipated to give a maximum of about 4.2 kilocal. from each force. The contribution to binding by a charge-transfer complex in a non-light excited state could be very small since these complexes that could form with any of the electron-donors or electron-acceptors present in a protein would have dissociation constants in the vicinity of 0.5-1, a negligible amount of energy (7). The inductive effect of the phenyl ring of I on the binding of the 4,6-diamino-*s*-triazine system is not readily measured, but intuitively it would be unlikely to increase binding by a factor greater than 10 (1.4 kilocal./mole). Thus, factors (a) and (b) alone most probably cannot account for the 4.5 kilocal./mole in increased binding when phenyl (I) is substituted for methyl (II). Since the *n*-butyl group (IV) can bind one-third as well as phenyl (I) and isoamyl (III) twice as well as phenyl (I) (Table I), it is clear that factors (c) and (d) could readily account for phenyl binding; note that factors (a) and (b) do not exist when II is compared with III or IV.

If the phenyl group of I does complex to a non-

polar region of dihydrofolic reductase, then ionized groups attached to the phenyl ring should cause a repulsion from this hydrophobic region. Note that insertion of a *p*-carboxyl group (V) or a *m*-carboxyl group (VI) causes about a 10,000 and 1000 fold loss in binding, respectively, compared to the parent phenyl analog (I); that this repulsion is due to a repulsive interaction of the anionic group on the inhibitor with an anionic group on the enzyme is therefore highly unlikely since such a repulsion should be position sensitive. Furthermore, if such an anionic-anionic repulsion did exist, then the *p*-aminomethyl derivative (VII) which is fully protonated at *p*H 7.4, should be a more powerful inhibitor than the parent phenyl analog (I) due to the attraction of the cationic group of VII to the supposed anionic group on the enzyme. Rather than being a better inhibitor than the parent phenyl derivative (I), the

TABLE I

Inhibition of Dihydrofolic Reductase By

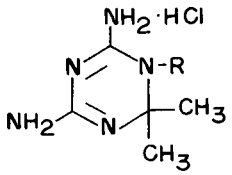


Compound No.	R	μM Conc. for 50% Inhibition (a)	Hammett σ Constant (b)	Hansch π Constant (c)
I	C_6H_5-	0.11 (d)	0	0
II	CH_3-	220 (d)		
III	*i*-C_5H_{11}-	0.058 (d)		
IV	*n*-C_4H_9-	0.36 (d)		
V	*p*-$C_6H_4COO^-$	1100 (e)	0	-0.28 (f)
VI	*m*-$C_6H_4COO^-$	110	0	-0.28 (f)
VII	*p*-$C_6H_4CH_2NH_3^+$	10	weak +	large - (g)
VIII	*p*-$C_6H_4COOC_2H_5$	42	+0.45	-0.01
IX	*p*-$C_6H_4CH_2NHCOCH_3$	0.11	weak -	-0.5 (h)
X	*m*-$C_6H_4NO_2$	0.072	+0.71	-0.28
XI	*m*-$C_6H_4CF_3$	0.080	+0.43	+1.1
XII	*p*-$C_6H_4C{\equiv}N$	8.0	+0.66	-0.57
XIII	*p*-$C_6H_4N(CH_3)_2$	0.98	-0.20	+0.18
XIV	*m*-$C_6H_4CH_3$	0.078	-0.07	+0.56
XV	*p*-C_6H_4-C_4H_9-*n*	0.064	-0.12	+1.9
XVI	*p*-C_6H_4-C_6H_5	160	-0.01	+1.9 (i)
XVII	*m*-C_6H_4-C_6H_5	1.3	+0.06	+1.9
XVIII	*m*-C_6H_4Cl	0.0085 (j)	+0.23	+0.71
XIX	*p*-C_6H_4Cl	0.44 (j)	+0.37	+0.71
XX	*m*-C_6H_4Br	0.0085 (j)	+0.22	+0.86
XXI	*p*-$C_6H_4CH_2C_6H_5$	0.040	-0.1 (k)	+2.4 (l)

(a) Dihydrofolic reductase was a 45-90% of saturation ammonium sulfate fraction, isolated and assayed with 6 μM dihydrofolate and 12 μM TPNH in 0.05 *M* Tris buffer at *p*H 7.4 as previously described (9); the technical assistance of Maureen Baker, Shirley Humphrey, and Karen Smith with these assays is acknowledged. (b) For the substituent on the 1-phenyl group of the dihydro-*s*-triazine; data from reference 10. (c) For the substituent on the 1-phenyl group of the dihydro-*s*-triazine; data from reference 11. π is a log function and a negative value is more soluble in water than octanol and a positive value is *vice versa*. (d) Data for reference 5. (e) NSC-3075; we wish to thank Dr. Harry B. Wood, Jr., Cancer Chemotherapy National Service Center for this sample. (f) Measurement for COOH; COO^- which exists at *p*H 7.4 would be expected to be much more negative. (g) This amine group is fully protonated at *p*H 7.4 and would be expected to have a large negative value. (h) Estimated from values recorded for CH_3-, C_2H_5-, and CH_3CONH-. (i) Estimated to be the same as *m*-C_6H_5-. (j) Data from reference 12. (k) Estimated from the relative sigma-values of *p*-methyl and *p*-phenyl (10). (l) Estimated by addition of the values for methyl and phenyl (11).

TABLE II

Physical Constants Of



Compound No. (a)	R	Method (b)	Yield %	m.p. °C	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VI	*m*-C_6H_4COOH	A	50	209-213 (c)	48.4	5.42	23.5	48.3	5.62	23.3
VII	*p*-$C_6H_4CH_2NH_2 \cdot HX$ (d)	B	80	201-202 (c)	41.2(d)	6.48	18.0	41.0	6.37	17.8
VIII	*p*-$C_6H_4COOC_2H_5$	A	37	181-183 (e, f)						
IX	*p*-$C_6H_4CH_2NHCOCH_3 \cdot H_2O$	A	55	206-208 (c)	49.0(g)	6.76	24.5	48.8	6.71	24.2
X	*m*-$C_6H_4NO_2$	A	80	191-192 (e, h)						
XI	*m*-$C_6H_4CF_3$	A	56	184-186 (e, i)						
XII	*p*-$C_6H_4C{\equiv}N$	C	82	202-203 (c, d)	47.7	5.72	23.9	47.9	5.74	23.7
XIII	*p*-$C_6H_4N(CH_3)_2 \cdot HCl$	A	99	219-220 (c)	46.8	6.65	25.2	46.6	6.53	25.5
XIV	*m*-$C_6H_4CH_3$	A	63	202-204 (e, j)						
XV	*p*-C_6H_4-C_4H_9-*n*	A	76	194-196 (k)	58.1	7.81	22.6	58.3	7.67	22.8
XVI	*p*-C_6H_4-C_6H_5	A	62	204-207 (l)	61.9	6.11	21.2	62.1	6.29	21.3
XVII	*m*-C_6H_4-C_6H_5	A	76	197-198 (m)	61.9	6.11	21.2	61.7	6.30	21.0
XXI	*p*-$C_6H_4CH_2C_6H_5$	A	55	201-203 (m)	62.9	6.45	20.4	62.6	6.42	20.2

(a) All compounds had the expected infrared and ultraviolet spectra unless otherwise noted. (b) See experimental. (c) Recrystallized from methanol-ether. (d) Ethanesulfonic acid salt. (e) Recrystallized from ethanol-ether. (f) M.p. 189-191° has been recorded (14). (g) Monohydrate. (h) M.p. 204-206° has been recorded (15). (i) M.p. 191-193° has been recorded (16). (j) M.p. 212° has been recorded (17). (k) Recrystallized from isopropyl alcohol. (l) Recrystallized from absolute ethanol. (m) Recrystallized from absolute alcohol-petroleum ether (b.p. 60-110°).

aminomethyl analog (VII) is actually only about 1/100 as effective; the repulsion of both an anionic or cationic group from the enzyme which is relatively insensitive to position is considered to be strong evidence that the phenyl group is complexed hydrophobically, that is, both the solvated anionic (V) or cationic (VII) groups are repulsed. When the charge is removed from the *p*-carboxyl group of V by conversion to the ester, VIII, the ester is about a 260-fold better inhibitor than the carboxylate; similarly, when the charge is removed from the cationic ammonium group of VII by acetylation, the acetamido derivative (IX) is a 100-fold better inhibitor than the corresponding amine (VII) (Table I).

Inductive effects should be observable if either factors (a) or (b) also contribute to binding; however, it is difficult to separate completely these effects from additional hydrophobic attraction, repulsion of a hydrophilic group on the inhibitor from the hydrophobic region of the enzyme, or from steric interactions with the enzyme surface. If inductive effects are present, it should be possible to correlate these effects with the Hammett sigma-values (10) (Table I); the relative hydrophobic or hydrophilic values of the substituents can be estimated from the Hansch π values (11) (Table I). Note that introduction in the *m*-position of the strong electron-withdrawing nitro (X) or trifluoromethyl (XI) groups or the practically neutral methyl group (XIV) gave compounds with little change in affinity for the enzyme; in contrast, with the electron-withdrawing chloro (XVIII) and bromo (XX), binding to the enzyme was increased 13-fold. The two halogen compounds are therefore unique and there is no correlation between enzyme affinity and either π or sigma or combinations of the two. Since none of these structural changes caused any detrimental effects to binding, there is apparently no unfavorable interaction with the enzyme caused by these particular *m*-substituents.

The results with the *p*-substituents are more difficult to interpret. The possible additional hydrophobic bonding to - or conversely, steric interaction with - the enzyme by *p*-substituents was first studied with the phenyl (XVI) and *n*-butyl (XV) groups. The *p*-*n*-butyl group caused little change in affinity

showing there was neither appreciable additional hydrophobic bonding nor steric interaction with the enzyme. In contrast, the *p*-phenyl group (XVI) caused a tremendous 1500-fold loss in binding. Note that this phenyl group is obviously non-polar (+ π) and has essentially no sigma-value; further, note that XVI has about the same order of binding as the 1-methyl-*s*-triazine, II. Thus, all of the binding of the 1-phenyl group of I is lost when the *p*-phenyl group (XVI) is introduced. This result can only be attributed to a steric interaction of the *p*-phenyl group with the enzyme. Since the more conformationally flexible *n*-butyl group (XV) or acetamidomethyl group (IX) do not give any steric interaction with the enzyme, it is clear that the enzyme can tolerate an out of plane group in the *p*-position, but not a relatively long group in the same plane as the 1-phenyl group; it was previously noted that the 2-fluorenonyl group, which is planar, also gave an 800-fold loss in binding (13). Also note that the *p*-benzyl group (XXI), which places the two phenyl groups out of plane still gives as good an inhibitor as I. This planar steric interaction of a phenyl substituent was considerably lessened when the phenyl group was shifted to the *m*-position; only an 11-fold loss in binding occurred.

It is obvious that the first carbon of a *p*-group does not interact sterically, else the *p*-acetamidomethyl (IX) and *p*-*n*-butyl groups (XV) would lower the affinity of I for the enzyme; however, the steric interaction of the *p*-phenyl group could begin to occur at any point after the carbon joining to the *p*-position of the 1-phenyl. The *p*-cyano group (XII) which is in the plane of the 1-phenyl and the *p*-carbethoxy (VIII) which has its $-CO_2-$ moiety in the plane of the benzene ring may give poor inhibitors primarily because of this steric interaction. Although it is possible that part of this detrimental effect on binding may be due to the electron-withdrawing properties of the carbethoxy and cyano groups, not all of the effect can be due to this property, else the more electron-withdrawing cyano group (XII) should have given a poorer inhibitor than the *p*-carbethoxy group (VIII), rather than *vice versa*; the same argument can be advanced for the relative π-values of the two groups. The electron-withdrawing *p*-chloro group (XIX) causes a 4-fold loss in binding, which may be attributed to its electron-withdrawing effect on the *p*-position; the main objection to these inductive effects being an important factor still remains the lack of these effects at the *m*-position by the trifluoromethyl (XI) and nitro (X) groups. Furthermore, the electron-donating group, dimethylamino (XIII) in the *p*-position also decreases binding by a factor of about 9-fold. This result cannot be attributed to hydrophobic repulsion since the dimethylamino group has a $+\pi$ value and is too weakly basic to be protonated at *p*H 7.4; since there is no correlation between the dimethylamino and *p*-carbethoxy groups with their opposite sigma-effects, the only remaining explanation is that the bulky dimethylamino group has some steric interaction when XIII is complexed with the enzyme.

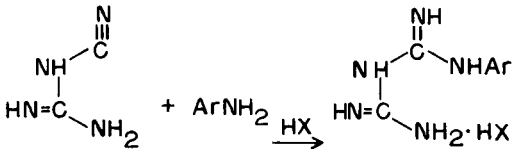
In summary, the data in Table I support the hypotheses (a) that the main contribution to binding by the aryl group of 1-aryl-*s*-triazines is by a combination of hydrophobic bonding and van der Waals forces, (b) inductive effects on enzymic complexing are relatively small, if at all present, and (c) steric inhibition of binding to the enzyme by in-plane substituents at the *p*-position of the 1-phenyl group can be large. It is highly probable that the aryl group of 5-aryl-2,4-diamino-6-alkylpyrimidines of the *Daraprim* type also is complexed with the enzyme mainly by hydrophobic bonding and van der Waals forces.

Further studies on the relative hydrophobic repulsion by the enzyme of a hydrophilic group on the aryl ring and steric interactions of coplanar *p*-substituents by dihydrofolic reductase in other species or tissues might lead to results of considerable value in chemotherapy if differences can be detected.

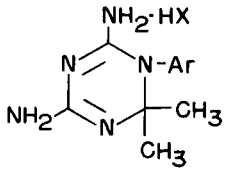
CHEMICAL METHODS

Synthesis.

Compounds VI, VIII-XI, and XIII-XVII were synthesized by the "three component" method of Modest (14), *i.e.*, the direct condensation of the arylamine (XIX) hydrochloride with cyanoguanidine (XVIII) in acetone. Unfortunately, with *p*-aminobenzonitrile,



XVIII XIX XX



XXII

p-aminobenzylamine, and 3-aminopyridine the reaction stopped at the intermediate biguanide stage (XX) due to the insolubility of the hydrochloride salt (XX); in the case of *p*-aminobenzonitrile, the more soluble ethanesulfonic acid salt proceeded satisfactorily to the desired *s*-triazine (XII) (Table I), but this modification still gave the intermediate biguanide (XX) with the latter two amines. Fortu-

nately, the dihydro-*s*-triazine system (XXII) is stable to hydrogenation in the presence of platinium oxide catalyst; under these conditions in the presence of additional ethanesulfonic acid, the desired *p*-aminomethylphenyl-*s*-triazine (VII) was obtained as its di-ethanesulfonate in 80% yield.

EXPERIMENTAL (18)

1-(*p*-Acetamidomethylphenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Hydrochloride (IX).

A mixture of 500 mg. (3 mmoles) of N-(*p*-aminobenzyl)acetamide (19), 269 mg. of cyanoguanidine, 2 ml. of acetone, and 0.25 ml. (3 mmoles) of 12 *N* aqueous hydrochloric acid was refluxed with magnetic stirring for 17 hours during which time an oily layer separated. The mixture was spin-evaporated *in vacuo*; the crystalline residue was triturated with acetone; yield, 881 mg. (91%), m.p. 197-200°. Recrystallization from methanol-ether gave 532 mg. (55%) of white crystals, m.p. 206-208°; λ max 243 mμ; ν max 3350, 3100 (NH); 1665, 1590-1620, 1540, 1520 cm^{-1} (C=O, $C=NH^+$, C=N, C=C, NH).

For analytical data see Table II; other compounds prepared by this method A are listed in Table II.

1-(3-Pyridyl)biguanide Dihydrochloride.

A mixture of 942 mg. (10 mmoles) of 3-aminopyridine, 900 mg. (10.7 mmoles) of cyanoguanidine, 2 ml. of absolute ethanol, 1 ml. of acetone and 1.68 ml. of 12 *N* aqueous hydrochloric acid was refluxed with magnetic stirring for 17 hours during which time the product separated. The product was collected on a filter and washed with acetone; yield, 592 mg. (20%), m.p. 228-230°. Recrystallization from methanol-ether gave the analytical sample as white crystals, m.p. 237-239°; λ max 250 mμ (broad); ν max 3350, 3100 (NH); 2720, 2650, 2050, 1900 (NH^+); 1650, 1625, 1550, 1530, 1520 (C=N, C=C, NH); 890, 810 cm^{-1} (pyridyl CH).

Anal. Calcd. for $C_7H_{10}N_6 \cdot 2HCl$: C, 33.5; H, 4.82; N, 33.5. Found: C, 33.7; H, 4.97; N, 33.4.

The same product was obtained if the acetone was omitted in the reaction (20).

1-(*p*-Cyanophenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Ethanesulfonate (XII).

A mixture of 236 mg. (2 mmoles) of *p*-aminobenzonitrile, 220 mg. (2 mmoles) of ethanesulfonic acid, 4 ml. of acetone, and 180 mg. (2.14 mmoles) of cyanoguanidine was refluxed with magnetic stirring for 18 hours during which time the product separated. The product was collected on a filter and washed with acetone; yield, quantitative, m.p. 199-200°. Recrystallization from methanol-ether with the aid of Norite gave white crystals, m.p. 203-204°; ν max 3400, 3150 (NH); 2220 (C≡N); 1670, 1650, 1610, 1595, 1550, 1525 ($C=NH^+$, C=N, C=C, NH); 1160, 1030 cm^{-1} (SO_3-); this compound did not give a distinct ultraviolet absorption maximum in water, but in 3 *N* HCl had λ max 237, 274, 282 mμ.

See Table I for analytical data; this is method C.

1-(*p*-Aminomethylphenyl)-4,6-diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Bis-ethanesulfonate (VII).

To a solution of 1.06 g. (3 mmoles) of XII in 100 ml. of 90% ethanol was added 0.33 g. (3 mmoles) of ethanesulfonic acid and 60 mg. of platimum oxide catalyst. The mixture was shaken with hydrogen at 2-3 atm. for 3 hours when reduction was complete. The filtered solution was spin-evaporated *in vacuo*. Recrystallization of the residue from methanol-ether gave 1.12 g. (80%) of white crystals, m.p. 201-202°, which was unchanged on further recrystallization. The compound showed λ max 242 mμ and ν max 3350, 3100 (NH); 1670, 1650, 1600, 1550, 1520 ($C=NH^+$, C=N, C=C, NH); 1180, 1035 (SO_3-); no C≡N near 2220 cm^{-1}.

See Table II for analytical results; this is method B.

REFERENCES

(1) This work was supported by Grant Nos. CA-05867 and CA-06624 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series, see B. R. Baker and J. H. Jordaan, *J. Pharm. Sci.*, 54, November (1965).

(3) V. M. Doctor, *J. Biol. Chem.*, 222, 959 (1956).

(4) T. H. Jukes and H. P. Broquist, in R. M. Hochster and J. H. Quastel, "Metabolic Inhibitors," Academic Press, Inc., New York, 1963, pp. 481-534.

(5) B. R. Baker, B.-T. Ho, and D. V. Santi, *J. Pharm. Sci.*, 54, 1415, (1965); paper XXVII of this series.

(6a) H. Kauzmann, *Advan. Protein Chem.*, 14, 1 (1959); (b) R. A. Wallace, A. N. Kurtz, and C. Niemann, *Biochemistry*, 2, 824 (1963); (c) G. Nemethy and H. A. Scheraga, *J. Phys. Chem.*, 66, 1773 (1962); (d) B. Belleau and G. Lacasse, *J. Med. Chem.*, 7, 768 (1964); (e) J. B. Jones, T. Kunitake, C. Niemann, and G. E. Hein, *J. Am. Chem.*, 87, 1777 (1965).

(7a) E. M. Kosower, "Molecular Biochemistry," McGraw-Hill Co., Inc., New York, 1962, pp. 180-195; (b) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964.

(8) B. R. Baker and H. S. Shapiro, *J. Med. Chem.*, 6, 664 (1963), paper IX of this series, have considered this type of explanation for the mode of binding of some 6-phenylpyrimidines to folic reductase.

(9) B. R. Baker, B.-T. Ho, and T. Neilson, *J. Heterocyclic Chem.*, 1, 79 (1964).

(10a) M. Charton, *J. Org. Chem.*, 28, 3121 (1963); (b) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, Inc., New York, 1940, pp. 184-207.

(11) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964).

(12) B. R. Baker and B.-T. Ho, *J. Pharm. Sci.*, 53, 1137 (1964); paper XVI of this series.

(13) B. R. Baker and B.-T. Ho, *J. Heterocyclic Chem.*, 2, 72 (1965); paper XXIII of this series.

(14) E. J. Modest, *J. Org. Chem.*, 21, 1 (1956).

(15) A. F. Crowther, British Patent 709,906 (1954); *Chem. Abstr.*, 49, 9046 (1955).

(16) M. W. Fisher, German Patent 1,118,790 (1961); *Chem. Abstr.*, 56, 15524 (1962).

(17) B. Roth, R. B. Burrows, and G. H. Hitchings, *J. Med. Chem.*, 6, 370 (1963).

(18) Melting points were taken on a Fischer-Johns apparatus, and those below 230° are corrected. Ultraviolet spectra were determined in water with a Perkin-Elmer 202 recording spectrophotometer. Infrared spectra were determined in KBr pellets with a Perkin-Elmer 137B recording spectrophotometer. All compounds in Table I gave ultraviolet and infrared spectra in agreement with their assigned structures; note the special conditions for the ultraviolet spectrum of XII in the experimental.

(19) H. H. Fox, *J. Org. Chem.*, 13, 438 (1948).

(20) F. H. S. Curd, and F. L. Rose, *J. Chem. Soc.*, 362 (1946).

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