[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

THE SO-CALLED ACYLANTHRANILS (3,1,4-BENZOXAZONES). I. PREPARATION; REACTIONS WITH WATER, AMMONIA, AND ANILINE; STRUCTURE[1]

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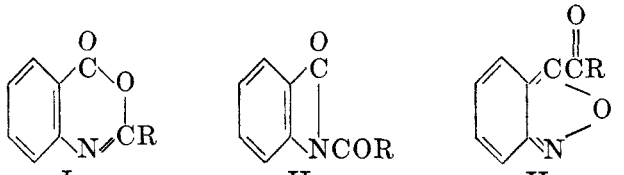
The class of compounds designated as acylanthranils,[3] or better 3,1,4-benzoxazones, has been represented hitherto by only 2-methylbenzoxazone (acetanthranil) and 2-phenylbenzoxazone (benzanthranil) and a number of derivatives of these with substituents mostly in the aromatic ring (1–12). The structure of the heteroelementary ring has not been decisively proved, some of the evidence being ambiguous (6, 13, 14, 15). A preference for the benzoxazone structure I is based partly on the improbability of the lactam structure II and of the *o*-quinonoid structure IIa, which last also seems inconsistent with the character of the acylanthranils. In the study reported herein there was developed a convenient



and fairly general procedure for preparation of 3,1,4-benzoxazones, of which eight new examples were obtained and characterized. Their chemical behaviors in several directions have been systematically examined, and new evidence as to structure is discussed.

Preparation of acylanthranils or 3,1,4-benzoxazones. The first representative of the class was made (16) by action of benzoyl chloride on anthranil, a method considered not suitable for extension owing to the instability of anthranil and the lack of a satisfactory method of preparation.[4] Bogert and Seil (5, 6) prepared acetanthranils by heating anthranilic acid or ring-substituted anthranilic acids with acetic anhydride, and by heating preformed N-acetyl- or N-benzoyl-an-

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[3] The acylanthranil names suggest methods of preparation from anthranil or anthranilic acid but their structural implications are deceptive. *Chemical Abstracts* treats these compounds as derivatives of 3,1,4-benzoxazone (Ring Index No. 947: 3,1,4H-benzoxazone), and for the most part they will be so named, sometimes in abbreviated form, in this paper. Grateful acknowledgement is made to Austin M. Patterson and Leonard T. Capell for advice as to nomenclature.

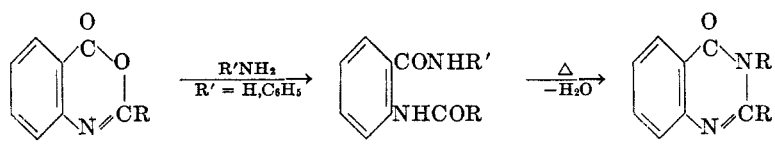
[4] Over-all yields of anthranil from *o*-nitrotoluene *via* *o*-nitrobenzaldehyde diacetate [Tsang, Wood, and Johnson, *Org. Syntheses*, **24**, 75 (1944); Vanino, *Präparative Chemie*, F. Enke, Stuttgart, 2nd Ed., Vol. II, 1923, p. 730] have barely exceeded 10%.

thranilic acids with acetic anhydride they obtained the corresponding acetanthranils and benzanthranils. Analogous procedures failed to yield 2-ethylbenzoxazones (propionanthranils) of demonstrated authenticity. The second procedure, judged to be the most promising of those available, was selected for study. Its usefulness depends upon whether or not acetic anhydride in general effects ring closure with acylanthranilic acids, and upon the extent to which acetic anhydride causes transacylation, leading to formation of acetanthranil, replacing wholly or in part the desired acylanthranil.

In the preparative procedure developed the acylanthranilic acid (Table VI) is heated with excess acetic anhydride, with slow distillation of the acetic acid formed in the reaction; after removal of excess acetic anhydride under reduced pressure the benzoxazone is isolated from the residue. In this way there were made the eleven benzoxazones listed in Table I. The method failed when R (formula I) was isobutyl, *n*-amyl, undecyl, and 3,5-dinitrobenzoyl. The optimum quantity of acetic anhydride was not determined in each case, but in the preparation of 2-methylbenzoxazone best results were obtained with about eight equivalents. The use of 90–95% ("practical") acetic anhydride instead of 99–100%, decreased yields only about 5%, but for difficult ring-closures it is probably necessary, and in general therefore advisable, to use acetic anhydride of high purity. Good yields of 2-ethylbenzoxazone and 2-*n*-propylbenzoxazone were obtained from anthranilic acid by interaction with propionic and *n*-butyric anhydrides, but the wider applicability of this method was not tested. Ring closure failed to occur when methyl anthranilate (instead of the acid) was heated with acetic anhydride. The product was N-acetylanthranilic ester or N,N-diacetylanthranilic ester, depending upon the severity of the treatment, but no 2-methylbenzoxazone was found.

Some reactions of 3,1,4-benzoxazones. Water. Bogert (12) reported the susceptibility of acetanthranil to hydrolysis; the initial cleavage to N-acetylanthranilic acid recalls that of benzoxazoles to acylaminophenols (18). This is a general characteristic of the benzoxazones, but their sensitivities to hydrolysis vary greatly. Formanthranil (3,1,4-benzoxazone) and acetanthranil (2-methyl-3,1,4-benzoxazone) are very sensitive, suffering deterioration due to atmospheric moisture[5] or to unsuspected moisture present in solvents. It appears that high 2-alkylbenzoxazones are increasingly stable toward hydrolysis, and that 2-arylbenzoxazones may be handled with no special precautions.

Ammonia and aniline. Stepwise conversion of acetanthranil and benzanthranil to substituted quinazolines (IV), *via* the *o*-acylaminobenzamides (III), by action of ammonia or primary amine was observed by Anschütz, *et al.* (19) and by Bogert, *et al.* (12):



I III IV

[5] Formanthranil is inherently unstable, and deteriorates under anhydrous conditions.

TABLE I

PREPARATION OF 3,1,4-BENZOXAZONES (ACYLANTHRANILS) BY ACTION OF ACETIC ANHYDRIDE ON N-ACYLANTHRANILIC ACIDS

3,1,4-BENZOXAZONE FORMULA I	MADE FROM[g]	YIELD[a], %	M.P., °C.	ANALYSIS			
					C	H	N
*3,1,4-Benzoxazone XIX (Formanthranil) R = H	V	56.8	43–44.4	Calc'd Found	65.3 65.2	3.43 3.53	9.53 9.62
2-Methyl- XX (Acetanthranil)	[b]	66.7	80–81[c]				
*2-Ethyl- XXI (Propionanthranil)	VI	74.7	85–86	Calc'd Found	68.5 68.5	5.18 5.10	8.00 8.09
*2-*n*-Propyl- XXII	VII	25.6	59–60	Calc'd Found	69.8 69.8	5.86 5.77	
2-Phenyl- XXIII (Benzanthranil)	X	81.0	123–124[d]				
*2-*o*-Tolyl- XXIV	XI	74.6	115	Calc'd Found	75.9 75.7	4.67 4.49	
*2-*p*-Tolyl- XXV	XII	58.5	154.5	Calc'd Found	75.9 75.7	4.67 4.48	
*2-*o*-Chlorophenyl- XXVI	XIII	91.0	139–140	Calc'd Found	65.3 65.1	3.13 3.07	
*2-*p*-Chlorophenyl- XXVII	XIV	89.4	190	Calc'd Found	65.3 65.2	3.13 3.03	
2-*o*-Nitrophenyl- XXVIII	XV	94.6	195–195.5[e]	Calc'd Found	62.7 62.5	3.01 3.14	
2-*p*-Nitrophenyl- XXIX	XVI	71.7	203[f]	Calc'd Found	62.7 62.6	3.01 2.88	
*2-(3-Pyridyl)- XXX	XVIII	80.8	153	Calc'd Found	69.7 69.8	3.60 3.43	

* Compound not reported previously.

[a] Yields of pure products.[b] Made from anthranilic acid.[c] Lit. m.p. 81–82° (5).[d] Lit m.p. 124.5° (12).[e] Lit. m.p. 197° (10).[f] Lit. m.p. 207° (12).[g] See Table VI.

These reactions were extended successfully to most of the benzoxazones available (Table I); the behaviors previously recorded, and those observed in the present study, permit the following conclusions.

Ammonia converts 3,1,4-benzoxazone and 2-methyl-3,1,4-benzoxazone, and presumably other 2-alkylbenzoxazones, to corresponding *o*-acylaminobenzamides (III) as isolable products when reaction occurs at or below room tempera-

ture, but moderate heating causes ring closure to IV. Conversion of benzanthranil and other 2-arylbenzoxazones to *o*-acylaminobenzamides (III; R = Ar; R′ = H) by action of ammonia requires moderate heating, and ring closure requires heating the dry amides above their melting points (20). The presence of an *ortho*

TABLE II

o-ACYLAMINOBENZAMIDES FROM 3,1,4-BENZOXAZONES BY ACTION OF AMMONIA

COMPOUND NO.	(FORMULA III; R′ = H) NAME	MADE FROM[f]	YIELD[a], %	M.P., °C.	ANALYSIS	C	H
XXXI	*o*-Formylaminobenzamide	XIX	33.1[b]	119–122[c]			
XXXII	*o*-Propionylaminobenzamide	XXI	[d]				
XXXIII	*o*-Butyrylaminobenzamide	XXII	[e]				
XXXIV	**o*-Toluylaminobenzamide	XXIV	24.4	217–218	Calc'd	70.8	5.55
					Found	71.0	5.21
XXXV	**p*-Toluylaminobenzamide	XXV	39.7	204–205	Calc'd	70.8	5.55
					Found	70.7	5.68
XXXVI	**o*-Chlorobenzoylaminobenzamide	XXVI	58.8	198–199	Calc'd	61.2	4.04
					Found	61.5	4.08
XXXVII	**p*-Chlorobenzoylaminobenzamide	XXVII	44.8	200.5	Calc'd	61.2	4.04
					Found	61.1	4.19
XXXVIII	**o*-Nitrobenzoylaminobenzamide	XXVIII	53.0	195	Calc d	58.9	3.89
					Found	59.0	3.94
XXXIX	**p*-Nitrobenzoylaminobenzamide	XXIX	61.5	235–236	Calc'd	58.9	3.89
					Found	58.9	3.77
XL	*Nicotinylaminobenzamide	XXX	53.9	211	Calc'd	64.7	4.60
					Found	64.7	4.43

* Compound not previously reported.

[a] Yields of pure products. [b] Reaction at 0°. [c] Lit. m.p. 123° (38). [d] Product was quinazolone XLII (Table III). [e] Product was quinazolone XLIII (Table III). [f] See Table I.

substituent in R prevented the ring closure. The essential results of the reactions with ammonia appear in Tables II and III.

Aniline reacts with benzoxazones at 100° or below to yield acylaminobenzamides (III; R′ = phenyl), which are readily prepared in this way. When R (in III) is aliphatic, conversion to IV requires heating to about 250°, but when R is aromatic, ring closure to IV at such temperature in the cases tested required the presence of zinc chloride. The presence of an *ortho*-substituent in R prevented or obstructed ring closure. In the two cases tested it was found that conversion of I

to IV in one operation was effected by condensation of the 2-alkylbenzoxazones with aniline at 150°, *i.e.*, at a temperature much lower than is required to cyclize the isolated intermediate III. Results of the experiments on the ring closure are given in Table V.

Transacylation experiments. Transacylation of N-acylanthranilic acids by heating with acetic anhydride under preparative conditions was observed to occur only with N-(3,5-dinitrobenzoyl)anthranilic acid and N-isovalerylanthranilic acid; the product in each case was 2-methylbenzoxazone (acetanthranil). Methyl

TABLE III

4-QUINAZOLONES FROM *o*-ACYLAMINOBENZAMIDES OR BENZOXAZONES BY ACTION OF AMMONIA

NUMBER	4-QUINAZOLONE FORMULA IV (R′ = H)	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
XLI	Quinazolone-4	XXXI	47.2	216–217[b]			
XLII	Ethylquinazolone-4	XXI	52.2	233[c]	Calc'd Found	68.9 68.8	5.79 5.55
XLIII	**n*-Propylquinazolone-4	XXII	43.1	200–201	Calc'd Found	70.2 70.2	6.43 6.31
XLIV	**p*-Tolylquinazolone-4	XXXV	38.1	241–242	Calc'd Found	76.3 76.2	5.12 5.25
XLV	**p*-Chlorophenyl-quinazolone-4	XXXVII	67.4	306[d]	Calc'd Found	65.5 65.3	3.54 3.35
XLVI	**p*-Nitrophenyl-quinazolone-4	XXXIX	68.3	351–352[d]	Calc'd Found	62.9 63.2	3.47 3.67
XLVII	*3-Pyridylquina-zolone-4	XL	41.5	276	Calc'd Found	69.9 69.8	4.06 3.94

* Compound not previously reported.

[a] Yield of pure product. [b] Previously reported: m.p. 216.5° (38). [c] Previously reported: m.p. 234° (39). [d] Observed; not corrected.

N-formylanthranilate suffered transacylation under more severe conditions (200°). Since none of the three compounds named was convertible to the benzoxazone by the preparative procedure, it may be concluded that transacylation may become noticeable or pronounced when ring closure to the benzoxazone is retarded or obstructed. Temperature may be a factor, for on heating N-formylanthranilic acid with propionic anhydride (b.p. 169°; which is considerably above the temperature of the usual reaction mixture) transacylation occurred and 2-ethylbenzoxazone was formed.

Transacylation involving displacement of the formyl group was induced in N-formylanthranilic acid by heating with acetic anhydride in presence of anhydrous sodium acetate or of γ-picoline. Only the formyl group could be thus re-

placed; when N-butyrylanthranilic acid or N-benzoylanthranilic acid was heated with acetic anhydride in presence of sodium acetate or with propionic anhydride, there was no evidence of transacylation.

The "transacylation" of benzoxazones (*i.e.*, conversion to other benzoxazones by action of suitable acid anhydrides) was tested by heating formanthranil with

TABLE IV

o-ACYLAMINOBENZANILIDES FROM 3,1,4-BENZOXAZONES BY ACTION OF ANILINE

NUMBER	*o*-ACYLAMINOBENZANILIDE FORMULA III; R′ = C_6H_5	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
XLVIII	*Propionaminobenzanilide	XXI	37.7	164	Calc'd Found	71.6 71.7	6.01 5.82
XLIX	**n*-Butyraminobenzanilide	XXII	58.4	151–152	Calc'd Found	72.3 72.1	6.43 6.61
L	Benzoylaminobenzanilide	XXIII	74.4	216–218[b]			
LI	**o*-Toluylaminobenzanilide	XXIV	39.9	194.5	Calc'd Found	76.3 76.5	5.49 5.33
LII	**p*-Toluylaminobenzanilide	XXV	51.8	220–221	Calc'd Found	76.3 76.1	5.49 5.50
LIII	**o*-Chlorobenzoylaminobenzanilide	XXVI	55.4	214–215	Calc'd Found	68.5 68.3	4.31 4.32
LIV	**p*-Chlorobenzoylaminobenzanilide	XXVII	52.5	236–237	Calc'd Found	68.5 68.6	4.31 4.22
LV	**o*-Nitrobenzoylaminobenzanilide	XXVIII	39.9	197	Calc'd Found	66.5 66.3	4.21 4.37
LVI	**p*-Nitrobenzoylaminobenzanilide	XXIX	53.3	207–208	Calc'd Found	66.5 66.5	4.21 4.20
LVII	*Nicotinylaminobenzanilide	XXX	61.8	248–249	Calc'd Found	71.9 71.7	4.78 4.37

* Compound not previously reported.

[a] Yield of pure product. [b] Previously reported: m.p. 218–219° (40).

excess acetic anhydride in presence of sodium acetate, and by heating formanthranil, acetanthranil, and benzanthranil with propionic anhydride. The results were negative.

It is concluded that, with the exception of N-acylanthranilic acids not convertible to benzoxazones, transacylation is not recognizably operative during the preparative procedure described later, *i.e.*, that ring closure, when it can occur, proceeds more rapidly than transacylation.

Evidence as to structure of acylanthranils. The *ultraviolet spectrum* of 2-methylbenzoxazone (acetanthranil) and, for comparison, the spectra of isatoic anhydride both in presence and absence of triethylamine (to induce rearrangement to the imidol structure which is essentially identical with the benzoxazone structure), and of N-acetylanthranilic acid, were determined and are shown simultaneously in Figure 1. The absorptions of acetanthranil and isatoic anhydride show sufficient similarity to suggest related structures. The absorptions of isatoic anhy-

TABLE V

3-PHENYL-4-KETOQUINAZOLINES FROM *o*-ACYLAMINOBENZANILIDES BY HEAT

NUMBER	3-PHENYLQUINAZOLONE FORMULA IV: R′ = C_6H_5; R	MADE FROM	YIELD[a], %	M.P., °C.	ANALYSIS		
						C	H
LVIII	*2-Ethyl	XLVIII	43.8	125–125.5	Calc'd	76.8	5.64
					Found	76.9	5.52
LIX	*2-*n*-Propyl	XLIX	53.2	120–121	Calc'd	77.3	6.10
					Found	77.2	5.95
LX	2-Phenyl	L	41.9	156–157[b]			
LXI	*2-*o*-Tolyl	LI	16.1	179–180	Calc'd	80.7	5.16
					Found	80.6	5.20
LXII	*2-*p*-Tolyl	LII	54.6	178	Calc'd	80.7	5.16
					Found	80.8	5.06
LXIII	*2-*p*-Chlorophenyl	LIV	39.8	177	Calc'd	72.2	3.94
					Found	72.1	3.72
LXIV	*2-*p*-Nitrophenyl	LVI	43.2	224–225	Calc'd	70.0	3.82
					Found	70.1	3.64
LXV	*2-β-Pyridyl	LVII	57.7	175–176.5	Calc'd	76.2	4.38
					Found	76.1	4.36

* Compound not reported previously.

[a] Yield of pure product. [b] Previously reported: m.p. 158–159° (41).

dride in neutral and in alkaline environments are identical, indicating either failure of triethylamine to cause sensible shift to the imidol form or failure of the imidol structure to cause absorption within the range of energy levels of the light employed. The absorption of N-acetylanthranilic acid shows no close similarity to that of either isatoic anhydride or acetanthranil.

The *infrared absorption spectrum* of acetanthranil is shown in Figure 2. No features capable of unequivocal interpretation in terms of structure are recognizable in absence of data for compounds of related structures. A broadening of the absorption of the carbonyl group in the 1700 cm^{-1} region may be attributable to the effects of other groupings which absorb frequencies somewhat lower or

TABLE VI

N-ACYLANTHRANILIC ACIDS

NUMBER	COMPOUND N-···ANTHRANILIC ACID	REFERENCE FOR PREP.	YIELD, %	M.P., °C.	ANALYSIS			
						C	H	N
V	Formyl	[a]	90	167[b]	Calc'd	58.2	4.28	
					Found[c]	58.1	4.31	
VI	Propionyl	23	71.3	114–115[d]				
VII	*n-Butyryl	24	32.6	118–118.5	Calc'd	63.7	6.33	6.76
					Found	63.1	6.19	6.72
VIII	Isovaleryl	24	33.5	115–116[e]				
IX	*n*-Caproyl	24	32.8	99–103[f]				
	Lauryl	24	40.8	92	Calc'd	71.4	9.15	
					Found	71.6	9.01	
X	Benzoyl	24	99.2	182–183[g]				
XI	*o-Toluyl	24, 26, 27	31.6	193–194	Calc'd	70.6	5.13	
					Found	70.5	5.20	
XII	*p-Toluyl	24, 26, 27	82.5	193–194	Calc'd	70.6	5.13	
					Found	70.5	5.24	
XIII	*o-Chlorobenzoyl	24, 27	59.6	186.5–187	Calc'd	61.0	3.66	
					Found	60.5	3.48	
XIV	*p-Chlorobenzoyl	24, 27, 28	96.8	204–205	Calc'd	61.0	3.66	
					Found	61.0	3.65	
XV	*o*-Nitrobenzoyl	24, 27	57.0	234–235[h]				
XVI	*p*-Nitrobenzoyl	24, 27	77.5	235.5[i]				
XVII	*3,5-Dinitrobenzoyl	24[k]	54.7	208–209 dec.	Calc'd[j]	48.1	3.17	
					Found	48.4	3.03	
XVIII	*Nicotinyl	24, 29	71.0	263–264	Calc'd	64.5	4.16	
					Found	64.5	4.25	

* Compounds not previously reported.

[a] Preparative method described in text. [b] Lit. m.p. 168° (25). [c] Meyer and Bellman (25) reported the compound to be a hemihydrate; C, 55.2; H, 4.53. Compound V is anhydrous. [d] Lit. m.p. 117° (42). [e] Lit. m.p. 114–115° (43). [f] Lit. m.p. 94–95° (17). [g] Lit. m.p. 182° (24). [h] Lit. m.p. 239° (10). [i] Lit. m.p. 235.5° (12). [j] Calculated as monohydrate; recrystallized from aqueous ethanol. [k] 3,5-Dinitrobenzoyl chloride dissolved in diethyl ether.

somewhat higher. The side ring of structure I consists of such groupings, *viz.*, —O—C=O (1720–1750 cm^{-1}) and —C=N— (1580–1660 cm^{-1}), and might

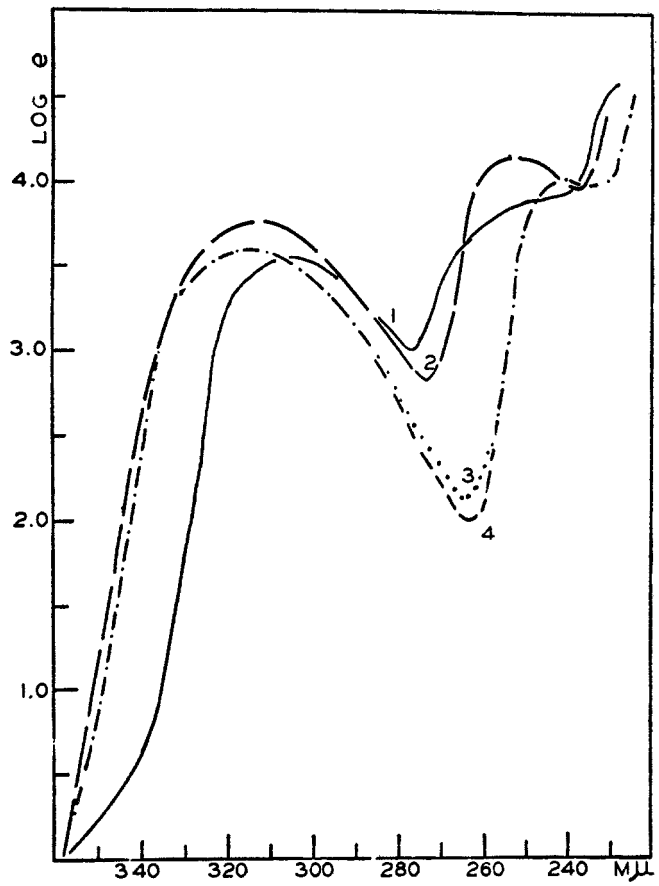


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA: of Acetanthranil (Curve 1), N-Acetylanthranilic Acid (Curve 2), Isatoic Anhydride (Neutral dioxane) (Curve 3), and Isatoic Anhydride (Alkaline dioxane) (Curve 4).

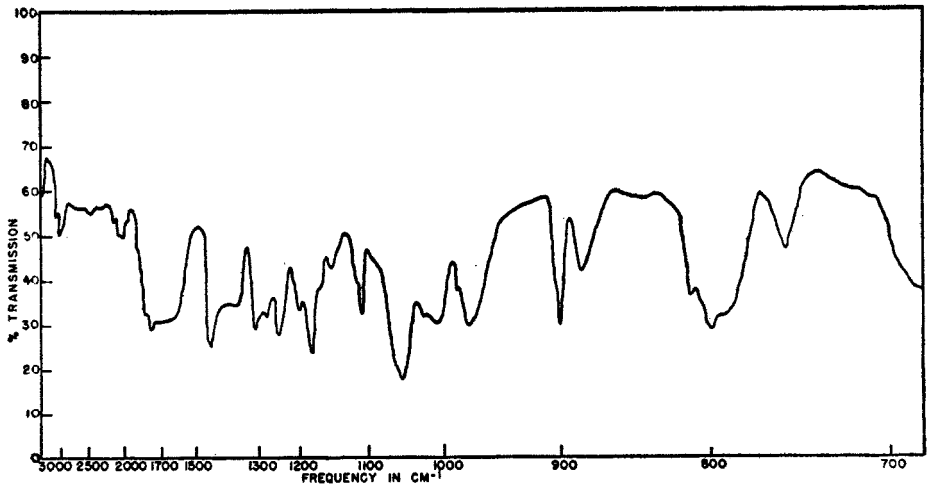


FIGURE 2. INFRARED ABSORPTION SPECTRUM OF ACETANTHRANIL

introduce the further effect of ring-strained carbonyl (1740–1800 cm^{-1}). As somewhat similar conclusions based on structures II or IIa can be reached, the interpretation of the infrared evidence is uncertain.

Certain of the chemical results permit inferences which support the belief that acylanthranils have the benzoxazone structure. 1. The failure to obtain acylanthranils from N-acylanthranilic acids in which R of the acyl group RCO contains a fairly long aliphatic chain (*n*-amyl, undecyl), or units which are obstructive sterically (isobutyl) or otherwise (3,5-dinitrobenzoyl), is more readily understandable if acylanthranils have the benzoxazone structure I than if the structure is II. In structure II it may be supposed that any interference of which the group R is capable will be diminished or absent because the carbonyl carbon separates R from the nitrogen atom involved in the ring closure. If the structure is I no such separation exists and any potentially restrictive character possessed by R will be operative in affecting the ease of ring closure. 2. The transacylation experiments yielded several results which show that structure II, against which the steric objections are strong but the chemical evidence is ambiguous, must be declared inadmissible on chemical grounds. The formyl group of N-formylanthranilic acid is replaced by either the acetyl or the propionyl group by heating with acetic anhydride in presence of sodium acetate or by heating with propionic anhydride; under the same conditions formanthranil is unchanged. If formanthranil has structure II, with the formyl group exposed in the same manner as in N-formylanthranilic acid, transacylation should occur as it does with N-formylanthranilic acid. The fact that formanthranil is unaffected justifies the conclusion that it contains *no formyl group attached to nitrogen* and that structure II is unacceptable. The stability of formanthranil towards acetic or propionic anhydride is entirely consistent with structure I, which could suffer "transacylation" only following ring rupture, which is unlikely, since the anhydride present in excess is actually an agent qualified to close the ring and since water, which opens the ring very readily, is necessarily absent.

It is believed that the foregoing arguments are sufficiently cogent to eliminate any residual doubt that the so-called acylanthranils are 3,1,4-benzoxazones of structure I.

EXPERIMENTAL

General. Melting and boiling points are corrected. Semimicro analyses for carbon and hydrogen (21, 22) and for nitrogen (23) were performed by Sarah M. Woods, of this laboratory.

N-Acylanthranilic acids were prepared by the method of Steiger (24), except that formylanthranilic acid was made as follows. A mixture of 68.5 g. (0.50 mole) of anthranilic acid in 500 ml. of benzene and 57 ml.)*ca.* 1.5 mole) of 99% formic acid was heated under reflux for three hours. The reaction mixture was chilled in ice, the caked solid was broken up, washed with benzene, and dried at 110°. The crude product (74.5 g., 90%) melted at 167°; recrystallization from ethyl acetate removed the color but did not change the m.p. The compound was water-free, and not the hemihydrate reported by Meyer and Bellman (25). Collected data for this and other acylanthranilic acids appear in Table VI.

Toluyl chlorides (*o*- and *p*-) were made from the nitriles (26) *via* the acids (27), of which *p*-chlorobenzoic acid was obtained by oxidation of *p*-chlorotoluene (28). Nitrobenzoyl

chlorides (*o*- and *p*-) were made from the acids (27) and nicotinyl chloride by the procedure of Berger, Alfriend, and Deinet (29).

Preparation of 3,1,4-benzoxazones (acylanthranils). General procedure. The all-glass apparatus comprised a 150-ml. round-bottom flask and a 10-inch Widmer column with electrically heated jacket, a condenser and a receiver with outlet protected by a calcium chloride tube. A mixture of 0.05 mole of N-acylanthranilic acid and 40.8 g. (0.4 mole) of 99–100% acetic anhydride was heated under total reflux for one hour, after which about 25 ml. was collected by slow distillation below 139°. Remaining acetic anhydride was removed under reduced pressure (water aspirator). On chilling the flask the residue solidified except in the case of formanthranil (isolation of which is outlined below) and in the trials which yielded no acylanthranils. The crude benzoxazone was dissolved in hot, dry[6] ethyl acetate, the solution was decolorized by Nuchar, and the filtered liquid was treated with *n*-hexane just short of turbidity and was chilled in an ice bath. A second crop was obtained by concentration of the mother liquor. The product was washed sparingly with cold ethyl acetate-*n*-hexane and was dried *in vacuo* over calcium chloride and paraffin shavings. In most cases a second crystallization yielded a pure product.

3,1,4-Benzoxazone (formanthranil). The dark viscous residue left after removal of acetic anhydride was distilled under 0.3 mm. pressure. The main portion distilled at 122° and solidified in the receiver, m.p. 43–44°. Formanthranil is readily hydrolyzed by atmospheric moisture. Upon standing in a stoppered flask for twenty-four hours a specimen showed the melting range 42–75°. Material kept in a drying pistol containing phosphorus pentoxide showed no change in melting point during seven days, but later acquired a yellow color and deteriorated. An attempt to obtain formanthranil by heating formylanthranilic acid with 99–100% formic acid (instead of acetic anhydride) was unsuccessful, and when formic acid was added to the usual reaction mixture (formylanthranilic acid and acetic anhydride) the general procedure yielded 3-(2′-carboxyphenyl)quinazolone-4, m.p. 274.5–275°. This was identified by analysis and later by mixed m.p. test (m.p. 273.5–274°) using a specimen of m.p. 276–277° prepared from N-anthranilylanthranilic acid[7] (30, 37). This compound is known to form (30) upon heating N-formylanthranilic acid under reduced pressure. Results of another unsuccessful attempt to make formanthranil are mentioned later.

2-Methyl-3,1,4-benzoxazone (acetanthranil) is best prepared from anthranilic acid and acetic anhydride by the general procedure. It should be crystallized with scrupulous exclusion of water, and may be purified also by sublimation at 70–75° and 0.03 mm. It should be stored in a desiccator.

Data for the twelve benzoxazones prepared in the manner described are presented in Table I. Only the first two were found to be noticeably affected by moisture; the others appear to be fairly stable compounds.

Benzoxazones were not obtained from the following N-acylanthranilic acids: isovaleryl, *n*-caproyl, lauryl, and 3,5-dinitrobenzoyl. The reaction residues were viscous and dark, and any solid materials isolated after prolonged operations were not benzoxazones. Thus isovalerylanthranilic acid gave a reaction mixture which after standing a month yielded some N-acetylanthranilic acid (m.p. 181–182°), formed probably by transacylation followed by incidental hydrolysis. From *n*-caproylanthranilic acid there was obtained a compound

[6] For the satisfactory purification of lower benzoxazones complete absence of water was found to be essential. Acetanthranil was dissolved for crystallization by heating with insufficient *n*-hexane (in which it is rather soluble) and adding ethyl acetate dropwise until a clear solution resulted.

[7] Heating with either formic acid or ethyl orthoformate converted anthranilylanthranilic acid to 3-(2′-carboxyphenyl)quinazolone-4 in high yield (44). By milder action of formic acid the product was *o*-formaminobenzoylanthranilic acid (m.p. *ca.* 211°; *Anal.*: Calc'd C, 63.3; H, 4.23; Found C, 63.4; H, 4.23) converted to the quinazolone (m.p. 276–277°) almost quantitatively on heating at the melting point. *Erratum.* In reference 37a, p. 63, Table I, column 2, following "anthranilic acid", the entry should be 150° instead of 50°.

of m.p. 144–144.5°, not identified (Analysis: C, 63.3; H, 5.91). From laurylanthranilic acid the only compound isolated was some unchanged starting material; 3,5-dinitrobenzoylanthranilic acid yielded some N-acetylanthranilic acid (m.p. 181–184°) by transacylation and hydrolysis.

Attempted use of acylanthranilic ester for benzoxazone synthesis. Methyl anthranilate, treated with acetic anhydride as in the general procedure, yielded only methyl N-acetylanthranilate. The same reactants, or methyl N-formylanthranilate and acetic anhydride, when heated at 200° yielded both methyl N-acetylanthranilate and methyl N,N-diacetylanthranilate. These results show that formylanthranilic ester suffered transacylation, and that considerable exhaustive acetylation occurred, but that conditions were not sufficiently severe to force ring closure.

Methyl N,N-diacetylanthranilate. Methyl N-formylanthranilate (10.0 g., 0.55 mole) and acetic anhydride (40.8 g., 0.4 mole) in a sealed tube were heated for six hours at 200°. After removal of acetic anhydride the residue yielded a product (3.5 g., melting range 60–78°) which after four recrystallizations from ethyl acetate-hexane melted at 66–67°. Analysis yielded data which indicate this compound to be methyl N,N-diacetylanthranilate.

Anal. Calc'd for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.57; N, 5.60; Sap. equiv., 78.3; Neut. equiv., 0.
Found: C, 61.3; H, 5.46; N, 5.67; Sap. equiv., 78.1; Neut. equiv., 0.

It appears that the m.p. 180° reported for this compound by Erdmann (31), and which is unexpectedly high for an amide incapable of association,[8] may be incorrect. The product of m.p. 66–67° was obtained also in an experiment with methyl anthranilate and acetic anhydride, and the two were shown by mixed m.p. test to be identical. In both experiments the mother liquors, including those from the recrystallizations, were examined further, leading to the isolation of solid products both of which after several crystallizations melted 98–99°; a mixed m.p. test showed them to be identical. Identification as *N-acetylanthranilic methyl ester* was established by the m.p. (33) and by analysis.

Anal. Calc'd for $C_{10}H_{11}NO_3$: C, 62.1; H, 5.70.
Found: C, 62.2; H, 5.67.

Reactions of 3,1,4-benzoxazones with ammonia. The benzoxazone (0.01) mole) was dissolved in the minimal absolute ethanol at a suitable temperature and anhydrous ammonia was bubbled into the solution for about an hour. To obtain *o*-acylaminobenzamides (III) the reaction with ammonia was conducted at a temperature below that which induces ring closure to quinazolone (IV). The products were isolated by concentration of the alcoholic solutions, and were generally pure after one recrystallization from ethyl acetate-hexane. In the case of 3,1,4-benzoxazone (formanthranil) chilling in an ice-bath was required, and temperatures below or near room temperature are needed with 2-methylbenzoxazone (acetanthranil) (19), 2-ethylbenzoxazone, and *n*-propylbenzoxazone, all of which were converted to quinazolones by ammonia at the temperature of boiling ethanol. Interaction with ammonia in boiling ethanol yielded the appropriate *o*-acylaminobenzamides (III) in good yields from the following benzoxazones: *o*- and *p*-tolyl, *o*- and *p*-chlorophenyl, *o*- and *p*-nitrophenyl, and 3-pyridyl. Essential data for these acylaminobenzamides appear in Table II.

To obtain the *2-substitutedquinazolones* (IV) the isolated *o*-acylaminobenzamide, in an open flask, was heated for thirty minutes at 240–250° (20) in a bath of Wood's metal. The residue was dissolved in the minimal ethyl acetate, the solution was treated with Nuchar, and to the hot filtrate was added hexane short of turbidity. The crystalline product in most cases was pure after one recrystallization. Data for the several quinazolones are collected in Table III.

Quinazolones were obtained in one operation from benzoxazone (formanthranil), 2-methylbenzoxazone, 2-ethylbenzoxazone, and 2-*n*-propylbenzoxazone by action of ammonia in boiling ethanol. Ring closure failed to occur at 250° with the following *o*-acylaminobenzam-

[8] The monoacetyl ester, presumably capable of association (32), melts at 100–101° (33). The fact that disubstituted amides melt lower than monosubstituted amides is familiar (32, 34).

ides: *o*-toluyl, *o*-chlorobenzoyl, and *o*-nitrobenzoyl, apparently due to interference by *ortho* substituents.

Reactions of 3,1,4-benzoxazones with aniline. To prepare the *o*-acylaminobenzanilide (III) a mixture of the acylanthranil (0.01 mole) and aniline (0.011 mole) in an open flask was heated for three hours on a steam-bath. The product was recrystallized from ethyl acetate-hexane after decolorization with charcoal, and was then substantially pure. For analysis a specimen of constant melting point was submitted to an additional crystallization. Preparative and analytical data appear in Table IV.

To prepare the *2-phenylquinazolones* (IV) the *o*-acylaminobenzanilide (III), when R was an alkyl group, was heated to 240–250° for thirty minutes; when R was aromatic the acylaminobenzanilide (0.01 mole) was mixed with about 3 mg. of anhydrous zinc chloride and the mixture was heated at 240–250° until evolution of gas ceased (about ten minutes). In preliminary trials it was found that heat alone failed to cause ring-closure of *o*-toluylaminobenzanilide at 250° or even at 300°. In each case the cooled melt was dissolved in the least hot ethyl acetate, and *n*-hexane was added until crystallization was well started, when the mixture was chilled in an ice-bath. The crystals were washed with eight 15-ml. portions of 10% aqueous ammonia, and were pure after an additional decolorization and recrystallization; samples for analysis were crystallized a third time. Preparative and analytical data for 3-phenylquinazolones appear in Table V.

Preparation of *quinazolones from benzoxazones* in one operation by heating the latter with aniline at an intermediate temperature was successful in the two trials made. When 2-ethylbenzoxazone (0.01 mole) and aniline (0.011 mole) were mixed and heated to 150–160° for thirty minutes there resulted a 67.8% yield of 2-ethyl-3-phenylquinazolone-4 of m.p. 125–126°. Similarly 2-*n*-propylbenzoxazone yielded 2-*n*-propyl-3-phenylquinazolone-4.

The interaction of 3,1,4-benzoxazone with aniline at 100° or at 160–170° produced a dark viscous oil from which no solid could be isolated. Ring closure failed to occur when R (formula III) was *o*-chlorophenyl or *o*-nitrophenyl, and when R was *o*-tolyl the yield of quinazolone was only 16%, again suggesting interference by *ortho* substituents.

Transacylation experiments. During preparation of benzoxazones other than 2-methylbenzoxazone the reaction mixtures yielded no 2-methylbenzoxazone, a result which does not establish its complete absence, though the fairly high yields of the expected benzoxazones shows that transacylation was at most probably inconsiderable. *Catalyzed transacylation* of *N*-formylanthranilic acid was effected as follows. A mixture of *N*-formylanthranilic acid (4.95 g., 0.03 mole), acetic anhydride (24.4 g., 0.24 mole) and anhydrous sodium acetate (0.49 g., 0.006 mole) was treated as in the general preparative procedure. The sodium acetate was removed, and the liquid was concentrated by passage of a stream of dry air until solid material separated. This was crystallized from ethyl acetate-hexane after treatment with Nuchar. The product melted at 78–80° and was identified as 2-methylbenzoxazone (acetanthranil) by mixed m.p.; the yield was 2.12 g. (44.7%). A similar experiment using γ-picoline (0.47 g., 0.005 mole) as catalyst yielded 1.36 g. (28.1%) of acetanthranil (m.p.79–80°), identified by mixed m.p. test.

No evidence of transacylation was observed in similar experiments in which *N*-*n*-butyrylanthranilic acid or *N*-benzoylanthranilic acid was heated with acetic anhydride either alone or with sodium acetate, or in which *N*-*n*-butyrylanthranilic acid was heated with propionic anhydride. Attempts to convert 3,1,4-benzoxazone or 2-phenylbenzoxazone to 2-ethylbenzoxazone by heating with propionic anhydride yielded none of the transacylated product, only starting materials being recovered.

Ultraviolet absorption spectra. The instrument used was a Beckman spectrophotometer (35). The solvent was dioxane purified as described by Fieser (36) followed by distillation through a 24-inch Vigreux column. Isatoic anhydride (37) was purified by recrystallization from 95% ethanol, then from dioxane, and finally by sublimation (170–180° at 0.02–0.03 mm.); the m.p. was 239–243°. Acetanthranil (2-methyl-3,1,4-benzoxazone) was crystallized three times from ethyl acetate-hexane, then sublimed (70–75° at 0.03 mm.), and was used at once, m.p. 81–82°. N-Acetylanthranilic acid was crystallized five times from ethyl ace-

tate and was dried in an Abderhalden apparatus, m.p. 184–185°. Triethylamine (E. K. Co. No. 616) was dried for twenty-four hours over pellet-form potassium hydroxide and was then distilled, b.p. 87–88°. The values for log E_m given below were determined for the following concentrations of solute: log E_m 1–2, 0.01 *M;* log E_m 2–3, 0.001 *M;* log E_m 3–4, 0.0001 *M;* log E_m 4–5, 0.00001 *M*. The wave lengths and intensities of the absorption maxima of isatoic anhydride, of isatoic anhydride in 0.01 *M* triethylamine solution, of 2-methyl-3,1,4-benzoxazone (acetanthranil), and of *N*-acethylanthranilic acid, are as follows.

COMPOUND	ABSORPTION WAVE LENGTH (m)	MAXIMA INTENSITY (LOG E_m)
Isatoic anhydride	315	3.58
	239	3.95
Isatoic anhydride in 0.01 *M* triethylamine	317	3.57
	242	3.96
2-Methyl-3,1,4-benzoxazone (acetanthranil)	305	3.54
	250	3.90
N-Acetylanthranilic acid	312	3.75
	252	4.14

Infrared absorption spectrum. Infrared absorption measurements were made with a Perkin-Elmer model 12B spectrometer. The sample of resublimed acetanthranil was melted on a salt plate for examination.

SUMMARY

1. A procedure is described for the preparation of 3,1,4-benzoxazones (acylanthranils) by dehydration of N-acylanthranilic acids with acetic anhydride. Eleven benzoxazones, eight of which are new, were so prepared. The method failed with the following N-acylanthranilic acids: isovaleryl, *n*-caproyl, lauryl, and 3,5-dinitrobenzoyl.

2. Transacylation by acetic anhydride was observed only with N-formylanthranilic ester and with several N-acylanthranilic acids which failed to yield benzoxazones. N-Formylanthranilic acid suffered transacylation by propionic anhydride, and by acetic anhydride in presence of sodium acetate or γ-picoline. Benzoxazones were not transposed by heating with unrelated acid anhydrides.

3. Under mild conditions 3,1,4-benzoxazones react with ammonia and with aniline to yield corresponding *o*-acylaminobenzamides and *o*-acylaminobenzanilides; sixteen of these not previously reported were made and characterized. By reaction at higher temperatures, or by heating N-acylaminobenzamides above 240°, or by so heating the N-acylaminobenzanilides in presence of zinc chloride, ring closure occurs yielding the 4-quinazolones; twelve new quinazolones are reported.

4. Certain of the results support the belief that the so-called acylanthranils have the benzoxazone structure.

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