STRUCTURE-ACTIVITY RELATIONSHIP OF CNS-DEPRESSANT QUINAZOL-4-ONES—PART II

TRUNCATED PORTIONS OF QUINAZOL-4-ONES

By

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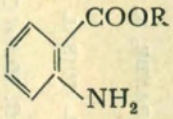
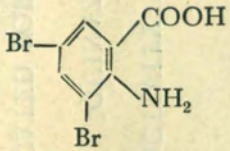
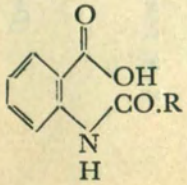
In part I of this study the structure-activity relationship of 2,3-disubstituted quinazol-4-ones has been described (Sareen *et al.*, 1959). As their CNS-depressant effect was traced to the presence of 3-phenyl-quinazol-4-one moiety, it was thought desirable to investigate if the constituent ortho-aminobenzoic acid (OAB) or some less truncated portion of the molecule was the basis of the activity. This paper communicates the screening of the various truncated portions of the active quinazol-4-ones for their hypnotic and anticonvulsant effects.

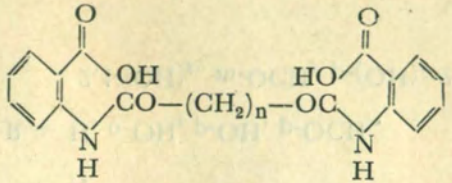
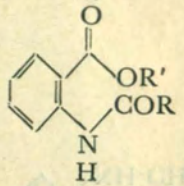
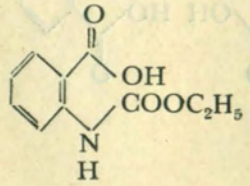
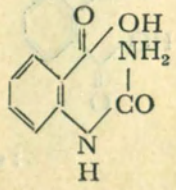
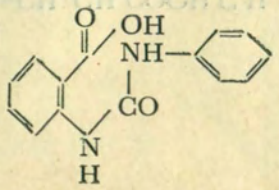
METHODS AND MATERIALS

The compounds were tested by using methods described in Part I of this study.

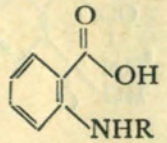
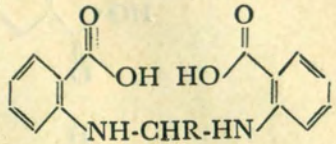
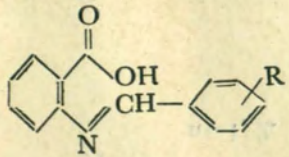
RESULTS

The results of screening of 45 compounds have been tabulated below. They were found to be devoid of any significant hypnotic or anticonvulsant effects.

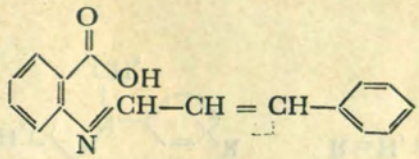
S. No.	Code No.	Name	Formulae	Hypnotic activity	Anticonvulsant activity (Percentage protectio
		A. Unsubstituted OAB :		Nil	Nil
1.	HAC–63	Anthranilic acid (and soluble salts like the hydrochloride and the Na-, K- and the NH_4-salts)	 R=H, CH_3	,,	,,
2.	HAC–64	Methyl anthranilate (and its hydrochloride)		,,	,,
3.	HAC–65	3,5-Dibromoanthranilic acid		,,	,,
		B. N-Acyl-anthranilic acids :			
4.	HAC–66	Formyl	 R=H, CH_3, C_2H_5	,,	,,
5.	HAC–67	Acetyl (and 3,5-dibromo derivative)		,,	,,
6.	HAC–68	Propionyl		,,	,,

7.	HAC-69	Malonyl	 n=1, 2.	"	"
8.	HAC-70	Succinoyl		"	"
9.	HAC-71	Benzoyl		R=CH_3, C_6H_5 R'=H, CH_3	" "
10.	HAC-72	N-Acetyl methylanthranilate			" "
11.	HAC-73	N-Benzoyl methylanthranilate			" "
12.	HAC-74	N-Carbethoxy anthranilic acid			" "
13.	HAC-75	N-Carbamyl anthranilic acid			" "
14.	HAC-76	N-(N'-Phenylcarbamyl)-anthranilic acid			" "

C. N-Alkyl- and alkylidene-anthranilic acids :

15.	HAC–77	Methyl		Nil	Nil
16.	HAC–78	Carboxymethyl	R=CH_3,CH_2COOH,C_6H_5	,,	,,
17.	HAC–79	Phenyl		,,	,,
18.	HAC–80	Methylene	 R = H, CCl_3	,,	,,
19.	HAC–81	Trichloroethylidene		,,	,,
20.	HAC–82	Benzylidene		,,	,,
21.	HAC–83	Salicylidene		,,	,,
22.	HAC–84	p-Hydroxybenzylidene		,,	,,
23.	HAC–85	Anisylidene		,,	,,
24.	HAC–86	Resorcylidene		,,	,,
25.	HAC–87	Vanillylidene	R = H, o-OH, p-OH, p-OCH_3,	,,	,,
26.	HAC–88	Veratrylidene	2,4-$(OH)_2$, m-OCH_3 p-(OH), 2,4-$(OCH_3)_2$	,,	,,

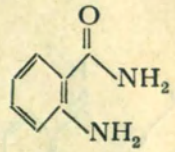
27. HAC–89 Cinnamylidene



" "

D. Amides and substituted amides :

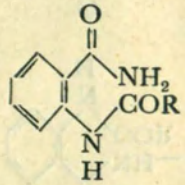
28. HAC–90 Anthranilamide



" "

29. HAC–91 o-Acetylaminobenzamide

30. HAC–92 o-Benzoylaminobenzamide



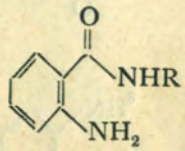
R = CH_3, C_6H_5

" "

" "

31. HAC–93 o-Aminobenzhydrazide

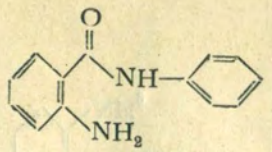
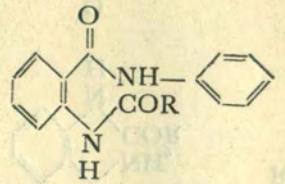
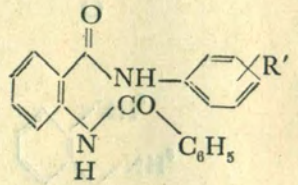
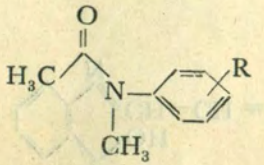
32. HAC–94 o-Aminobenzhydroxamic acid



R = NH_2, OH

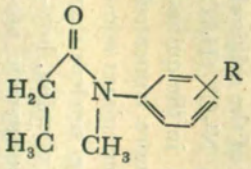
" "

" "

33.	HAC–95	Anthranilide			Nil	Nil
34.	HAC–96	o-Acetylaminobenzanilide		$R=CH_3, C_6H_5$	,,	,,
35.	HAC–97	o-Benzoylaminobenzanilide			,,	,,
36.	HAC–98	o-Benzoylamino-o-toluidide		$R'=o\text{-}CH_3$, p-OCH_3	,,	,,
37.	HAC–99	o-Benzoylamino-p-anisidide			,,	,,
38.	HAC–100	N-Methyl-acetanilide		R=H, o-CH_3	,,	,,
39.	HAC–101	N-Methyl-acet-o-toluidide			,,	,,

40. HAC-102 N-Methyl-propionanilide

41. HAC-103 N-Methyl-propion-o-toluidide

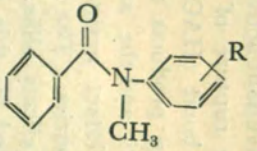


R=H, o-CH_3 " "

" "

42. HAC-104 N-Methyl-benzanilide

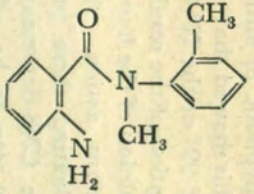
43. HAC-105 N-Methyl-benz-o-toluidide



R=H, o-CH_3 " "

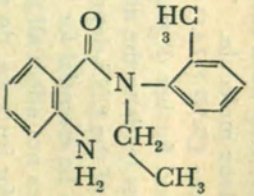
" "

44. HAC-106 N-methyl-anthranil-o-toluidide



" "

45. HAC-107 N-Ethyl-anthranil-o-toluidide



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DISCUSSION

The study of the above table shows that OAB (anthranilic acid), as free acid, soluble salts or ester, and its 6,8-dibromo-derivative (HAC-65) were found to be quite inactive. The same was true of the N-acyl (HAC 66-76) and the N-alkyl or alkylidene derivatives (HAC 77-89). Even HAC-76 which resembled N^3-phenyl-quinazol-4-ones more closely than other compounds of this series was inactive. The inactivity of HAC-81 showed that even the inherent CNS-depressant effect of chloral could be masked by reaction with OAB. Ortho-aminobenzoic acid thus resembles para-aminobenzoic acid in that the free acid and its ester are nontoxic (Hilderbrandt, 1903; Kleist, 1903) and inactive, while the introduction of a basic centre, like a diethylamino group, in the β-position of the ester confers on them local anaesthetic properties.

Conversion of OAB into its amides (HAC 90-94) or for a still closer resemblance to the N^3-phenyl-quinazol-4-ones, into anilides (HAC 95-107) could not bring back the hypnotic or anticonvulsant activities of the original quinazolone molecule. This showed that the rupture of the N^1-C^2 (HAC 106-7), the C^2-N^3 (HAC 96-99) or the N^3-C^4 bond (HAC-76) in the quinazolone and further degradation of the resulting products to more truncated fragments leads to the abolition of the hypnotic and the anticonvulsant components of the CNS-depressant action. An intact pyrimidine nucleus thus seems to be essential for eliciting these properties. The ring opening, however, does not affect all the CNS-depressant effects alike. Antipyretic properties, for instance, do not seem to be affected by this change as the compounds HAC-100—105 are known to possess antipyretic (and analgesic) actions (Fourneau, 1925; Berger, 1951).

SUMMARY

Truncated portions of 3-phenyl-quinazol-4-ones, as o-acylaminobenzanilide or N-methyl-anthranilide, and their further degradation products, as OAB, its acyl or alkyl derivatives and its amides, are devoid of the hypnotic and the anticonvulsant components of the CNS-depressant actions of the original molecule. An intact pyrimidine nucleus is essential for these activities. Antipyretic activity of 3-phenyl-quinazol-4-one, however, is not affected by degradation upto the anilide level.

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