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Review

Chemistry and Structure-Activity Relationships of Amphenone Analogues*

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Complete or partial inhibition of adrenal corticoid secretion has become an important goal of the medical and biological sciences. The progress in both qualitative and quantitative assay methods for steroid hormones enables the biochemist to measure alterations in the hormonal balance. Consequently, it seems to be feasible to search for compounds which may induce selective reversible or even irreversible changes in the hormonal pattern.

An extensive study has been made by chemists in producing alterations in the structure of the natural hormones in an effort to obtain compounds with a narrower spectrum of biological activity and a high intensity of the desired specific action. With regard to the corticoid hormones, most of these chemical changes were aimed at producing a high glucocorticoid activity. It should be noted here that one important feature of the evaluation of such 'tailor-made' hormones is their ability to diminish adrenocorticoid production *via* suppression of pituitary ACTH output.

Among the few non-steroidal synthetic compounds capable of exerting adrenal cortical suppression Amphenone B is the most broadly investigated substance. We have repeatedly reported on a variety of agents which we generally classify under the name of Amphenone analogues.

The preparation of Amphenone B itself was achieved *via* the illustrated pinacol–pinacolone type rearrangement.[1] The intermediate pinacol I was prepared by a bimolecular cathodic reduction of *p*-aminoacetophenone.[2]

* Bencze, W. L., Barsky, L. I., Allen, M. J. and Schlittler, E. *Helv. chim. Acta* **41**, 882 (1958). Also one of the present authors has discussed Amphenone analogues at the Gordon Research Conference on Medicinal Chemistry, New London, N.H., August 18–22, 1958.

Both aqueous hydrochloric acid and concentrated sulphuric acid effect the rearrangement of the pinacol I resulting in the exclusive migration of the *p*-aminophenyl group. Hence, structure (II), 3,3-bis-(*p*-aminophenyl)-2-butanone dihydrochloride has been assigned to Amphenone B.[3,4]

The rearrangement may be carried out by allowing an aqueous solution of the dihydrochloride of pinacol I to react at room

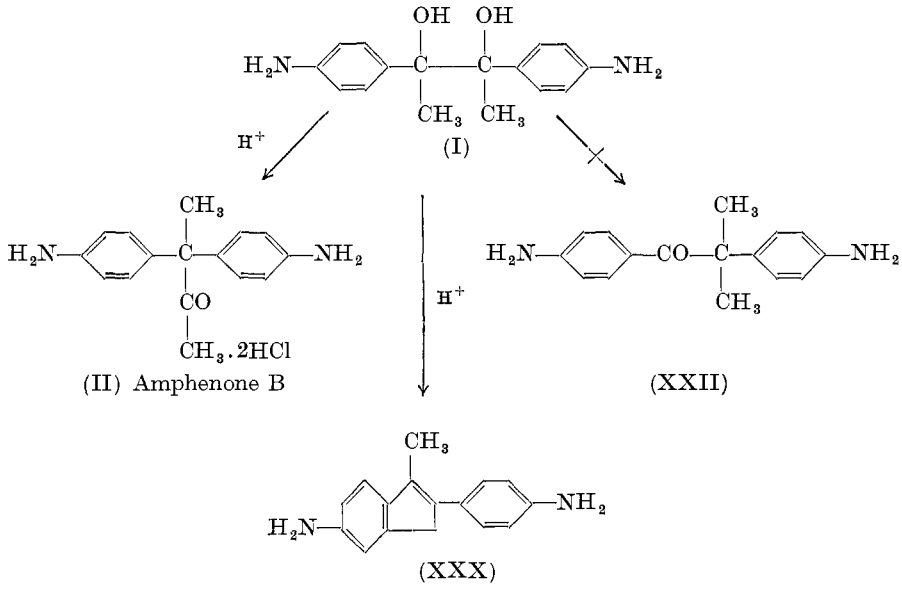
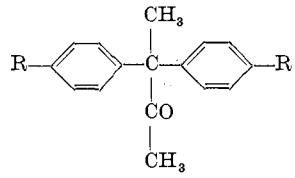


Fig. 1

temperature, or, more conveniently, by boiling the solution. This procedure gives ketone (II) in yields of 62 and 67 per cent, respectively. By increasing the concentration of the hydrochloric acid to 4 N, cyclodehydration is effected preferentially and the substituted indene (XXX) is obtained in 61 per cent yield together with a 30 per cent yield of (II). On the other hand, using concentrated sulphuric acid in the cold, cyclodehydration does not occur and Amphenone B is formed in 70 per cent yield. Ketone (XXII), isomeric to amphenone and derived by the migration of a methyl group, does not arise from the above rearrangement.

The effect upon the biological activity of Amphenone by introduction of substituents other than free amino groups into the two *para* positions of 3,3-diphenylbutanone was studied on the compounds shown in Table I.

Table I. *p*-Substituted 3,3-diphenylbutanones.



No.	R	Activity*
II	$N^+H_3Cl^-$ †[1]	Active
III	$N^+H(CH_3)_2Cl^-$ †[5]	Slightly active
IV	$N^+(CH_3)_3I^-$	Inactive
V	H †	
VI	OCH_3 †[6]	
VII	COOH †	
VIII	CN ‡	
IX	F ‡[7]	
X	Cl ‡[7]	Moderately active
XI	SO_2NH_2 ‡	Inactive

The following three compounds were also prepared: (XII) (R = Br), (XIII) (R = I) and (XIV) ($R = NO_2$). Due to their poor solubilities in solvents suitable for intravenous administration, the activity of these substances as adrenal cortical inhibitors could not be assessed properly.

* Reduction of concentration of 17-hydroxysteroids in adrenal vein blood. For detailed information about the biological evaluation of some selected compounds see the subsequent publication in this issue, page 407.

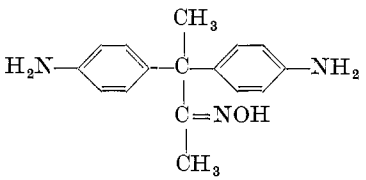
† Prepared from the corresponding *p*-substituted acetophenones *via* pinacol reduction and rearrangement.

‡ Obtained from Amphenone by Sandmeyer-type exchange reactions.

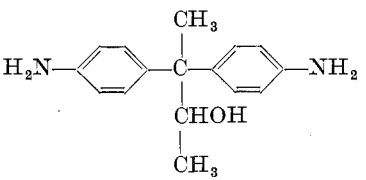
It is interesting to note that the *N,N'*-tetramethyl derivative of Amphenone, compound (III), demonstrated increased toxicity and decreased adrenocorticoid inhibitory activity when compared with (II). The dichloro substituted compound (X), structurally related to both Amphenone and the insecticide DDD, 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethane,[8] exhibited slight inhibitory activity when compared with that of (II). The sulphonamide derivative (XI) is an analogue of the German diuretic drug Nirexon,[9]

4,4′-disulphamyldiphenylmethane. The diuretic activity of (XI) however, was rather weak. None of the above compounds showed improvement in regard to their biological activity over Amphenone.

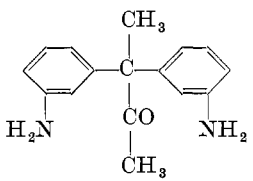
Such chemical changes as oximation (XV) or reduction (XVI) of the carbonyl group of Amphenone did not substantially alter the full spectrum of the biological activity of (II). However, shifting the amino groups to the *meta* position (XVII) caused complete loss of biological activity. Exchange of the two methyl groups of Amphenone for ethyl radicals (XVIII) proved to be of no advantage as the inhibitory activity was diminished.



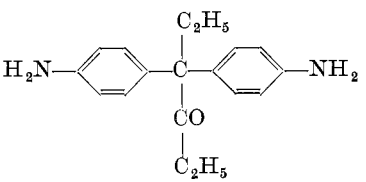
(XV)



(XVI)



(XVII)



(XVIII)

Compounds (XVII) and (XVIII) were prepared from *m*-aminoacetophenone and *p*-aminopropiophenone, respectively, by bimolecular pinacol reduction and subsequent rearrangement.

As indicated in Fig. 1, ketone (XXII), isomeric with Amphenone, could not be obtained from the parent pinacol I. The reaction scheme shown in Fig. 2 was chosen for its preparation.[10]

Treatment of di-(*p*-bromophenyl)cadmium with α-phenyl*iso*-butyryl chloride yielded 1-(*p*-bromophenyl)-2-methyl-2-phenyl-1-propanone. The aromatic bromine was exchanged for an amino group which subsequently was oxidized to the mononitro compound. Nitration and catalytic reduction led to the desired diamino pinacolone (XXII). The structure of (XXII) was

established through conversion to (XXIII) by a Sandmeyer reaction and comparison with a sample prepared from α-(*p*-chlorophenyl)*iso*butyryl chloride and di-(*p*-chlorophenyl)cadmium. The compounds listed in Table II were prepared in a similar fashion from organocadmium compounds and acid chlorides.[10]

From the diphenylbutanone series it was learnt (see Table I) that only compounds with chloro or basic substituents possessed

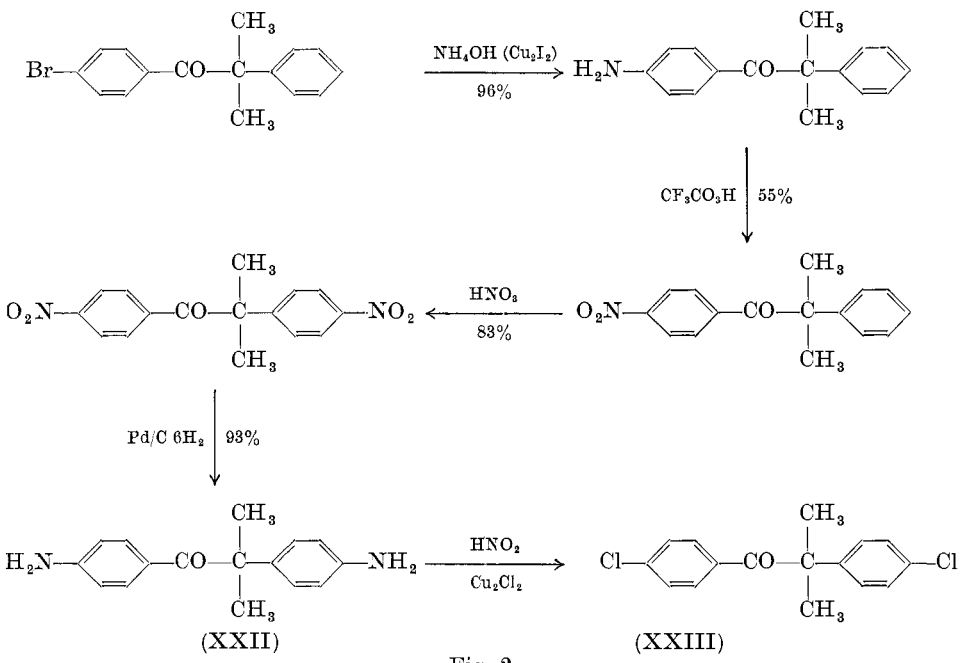
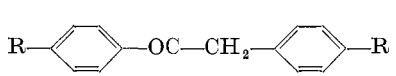


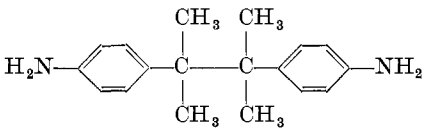
Fig. 2

Amphenone-like activity. Hence, only amino groups and halogens were introduced into the above α,α-dimethyldesoxybenzoin structure. It is of interest to note that one amino group on the benzoyl side (XXI), is sufficient to exert a corticoid suppression, whereas an amino group on the other side (XX), results in a very transient, if any, adrenal cortical inhibition, followed by a rise in the corticoid output.



(XXVII): R = H
(XXVIII): R = NH_2

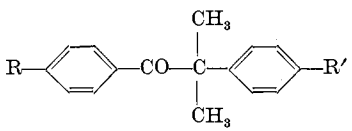
Desoxybenzoin (XXVII), like α,α-dimethyldesoxybenzoin (XIX), showed high Amphenone-like activity. These compounds were, however, more toxic than Amphenone. Surprisingly compound (XXVIII) showed very low activity in adrenocortical suppression.



(XXIX)

Compound (XXIX) had been reported in the literature[11] and was found to be practically inactive as an adrenal suppressant.

Table II. p,p'-Substituted α,α-dimethyldesoxybenzoins.



No.	R	R′	Activity
XIX	H	H	Active
XX	H	NH_2	Activity of short duration
XXI	NH_2	H	Similar to Amphenone
XXII	NH_2	NH_2	Similar to Amphenone
XXIII	Cl	Cl	Inactive*
XXIV	Cl	H	Active but more transient than II
XXV	Br	Cl	Inactive*
XXVI	Cl	NH_2	Resembles XX

* Because of poor solubility the biological test may have been inconclusive.

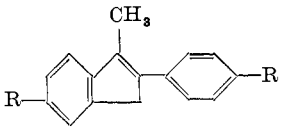
As pointed out previously, treatment of pinacol I with acid caused formation of increasing amounts of the cyclodehydrated product (XXX), a substituted indene derivative. Compounds of this type are listed in Table III.

Compound (XXXIV) was prepared from p-aminopropiophenone by pinacol reduction and cyclodehydration:[1] it was found to possess very little activity. Reduction of compounds (XXX) and (XXXI) led to the corresponding indane derivatives (XXXV) and (XXXVI). This partial saturation did not substantially

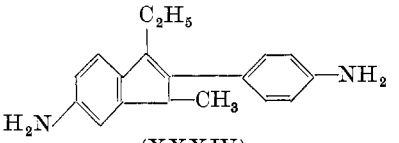
affect the activity, and maintained the relatively low toxicity of the parent compounds unchanged.

One startling correlation between chemical structure and biological effect should be mentioned here: dimethylation of the two amino groups of the indene derivative (XXX ⟶ XXXI) decreased the toxicity, while the same structural change in the diphenylbutanone series (II ⟶ III), on the contrary, increased the toxicity.

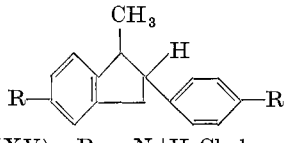
Table III. Indene derivatives.



No.	R	Activity
XXX	$N^+H_3Cl^-$ [1]	Slight activity
XXXI	$N^+H(CH_3)_2Cl^-$ [5]	Active
XXXII	$N^+(CH_3)_3I^-$	Inactive, very toxic
XXXIII	Cl	Inactive, poorly soluble



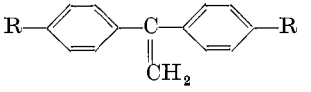
(XXXIV)



(XXXV): R = $N^+H_3Cl^-$[1]
(XXXVI): R = $N^+H(CH_3)_2Cl^-$

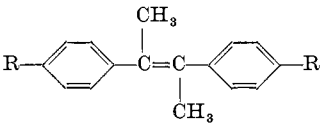
The secondary alcohol (XVI), obtained by reduction of Amphenone B, undergoes in an acidic medium a retropinacol rearrangement in which the *p*-aminophenyl group migrates to form a substituted stilbene.[1]

A Beckmann rearrangement in polyphosphoric acid was effected on the oxime (XV) of Amphenone B. The reaction took an abnormal course and a 1,1-diphenyl-substituted ethylene derivative was obtained.[3]



(XLII): R = NH_2
(XLIII): R = $N(CH_3)_2$

Table IV. Stilbene derivatives.

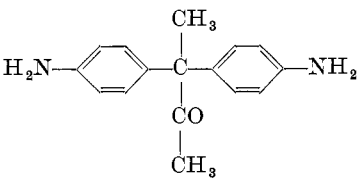


No.	R	Activity
XXXVII	$N^+H_3Cl^-$ [1]	Slight activity
XXXVIII	$N^+H(CH_3)_2Cl^-$	Slight activity
XXXIX	$N^+(CH_3)_3I^-$	Inactive
XL	4-Aminostilbene	Inactive
XLI	4,4′-Diaminostilbene	Inactive

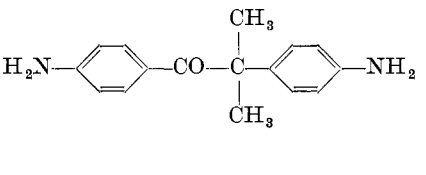
The last two compounds are practically inactive; generally the ratio of Amphenone-like activity to toxicity in this group was very unfavourable.

Compound (XLII) was found to be less toxic and nearly as active as Amphenone B. Compound (XLIII) was inactive.

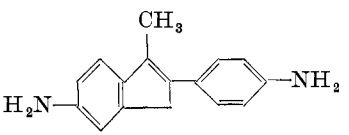
Fig. 3 briefly summarizes the five types of compounds discussed so far. *N*,*N*′-Tetramethylation of (XXX) and (XXXVII) has



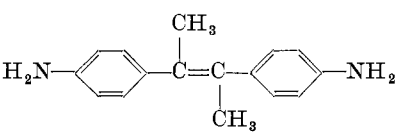
(II)



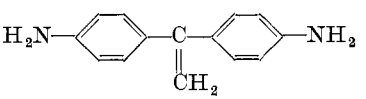
(XXII)



(XXX)



(XXXVII)

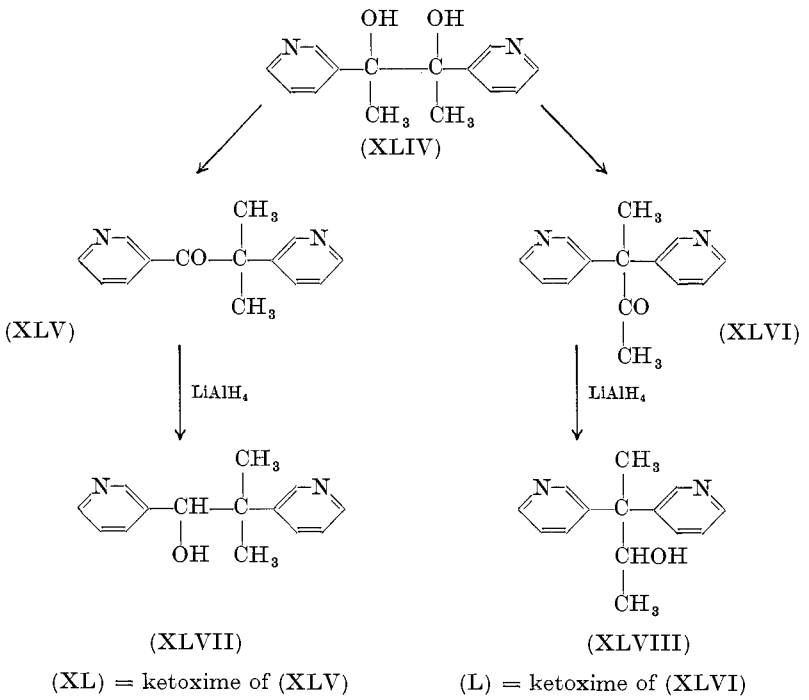


(XLII)

Fig. 3. The main representatives of active Amphenone analogues.

led to more favourable compounds; on the other hand *N*,*N*′-tetramethyl derivatives of (II) and (XLII) were less active and more toxic. In every instance the basically substituted compounds illustrated in Fig. 3 possessed the highest activity in regard to adrenal cortical suppression. It seemed to be reasonable, therefore, to investigate compounds based on the structures shown in Fig. 3, but carrying basic substituents other than the *p*-aminophenyl group. The second part of this report deals with Amphenone analogues containing pyridine rings.

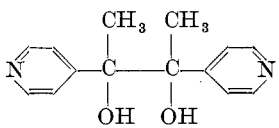
Our main procedure for the preparation of the pyridine type Amphenone analogues was essentially the same as used for Amphenone B itself. The 2,3- and 4-acetylpyridines were reduced electrolytically[12-14] or photochemically to their corresponding pinacols and these rearranged to yield the desired pinacolone type ketones.[15] Among the several rearranging agents checked, concentrated sulphuric acid gave the most satisfactory results.



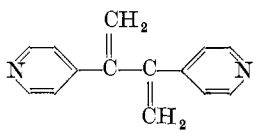
Upon rearrangement of pinacol (XLIV) both of the isomeric ketones (XLV) and (XLVI) were obtained in 50–55 per cent overall yield. The ratio of the isomers was found to be 70 per cent of (XLV) and 30 per cent of (XLVI). Hence, the intrinsic migratory aptitude[16] of the 3-pyridyl group was $0 \cdot 43 \pm 0 \cdot 04$ when compared with the migration of the methyl group.

Compound (XLV), 1,2-bis(3-pyridyl)-2-methyl-1-propanone, was chosen for broad biological and clinical investigation and the code number Su–4885 was assigned to it.[17]

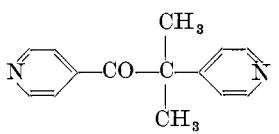
The isomeric ketone (XLVI) was found to be qualitatively and quantitatively similar to (XLV) in its adrenal inhibitory effect. Reduction or oximation of the two isomeric ketones (XLV) and (XLVI) did not cause any marked change in the intensity of the adrenocortical inhibitory effect.



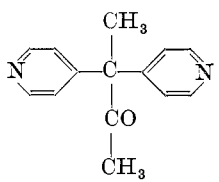
(LI)



(LII)



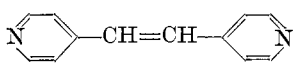
(LIII)



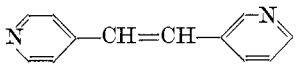
(LIV)

Rearrangement of the 4-pyridyl pinacol (LI), as in the case of the 3-pyridyl isomers, resulted in the two ketones (LIII) and (LIV), in lower yield but in the same 7 : 3 ratio. However, in this instance a considerable quantity of the pinacol underwent double dehydration to yield the dipyridylbutadiene (LII). The four isomeric pinacolone type ketones (XLV, XLVI, LIII and LIV) showed the highest amphenone-like activity so far encountered, whereas the two isomeric pinacols (XLIV) and (LI), from which the four ketones had been prepared, possessed only moderate activity. The butadiene derivative (LII) was less active than the ketones and more toxic.

The following four commercial products (Aldrich Chemical Company Inc. Milwaukee, Wisconsin) have also shown moderate activity but exhibited disturbing toxic manifestations.



(LV)



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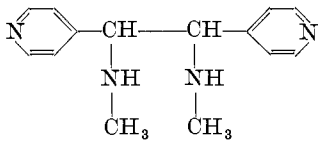
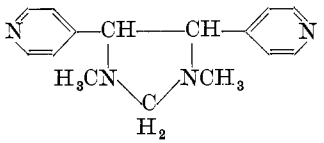
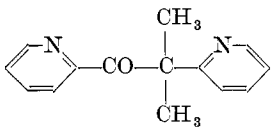


(LVII)



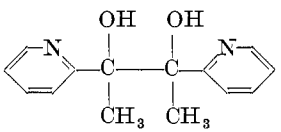
(LVIII)

Generally, the 2-pyridyl analogues of the highly active 3- and 4-pyridyl compounds have shown no adrenal cortical inhibitory activity. Some of these inactive compounds are listed below (LIX–LXII).

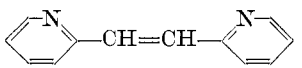


(LIX)

(LX)



(LXI)



(LXII)

Ketone (LIX) was prepared by rearrangement of pinacol (LXI) in concentrated sulphuric acid. The isomeric dipyridylbutanone type ketone was not present in the reaction mixture.

In regard to the diversity of the chemical structures of the compounds possessing Amphenone-like activity we are reminded of the estrogens: folliculoid activity can be associated with many compounds belonging to considerably different chemical groups.[18,19]

It is hoped that through the combined efforts of pharmacologists and chemists this very interesting chapter of modern endocrinology will be enriched with a number of useful Amphenone analogues.

Summary. The chemistry and the results of the biological screening of 62 compounds as adrenal cortical inhibitors are presented. Several basic pinacolone type ketones and unsaturated compounds can suppress production of corticoids by the adrenal cortex. Some aspects of the interrelation of structural changes and biological activity are discussed.

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