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Diaryl Succinimides as Amphenone Analogues

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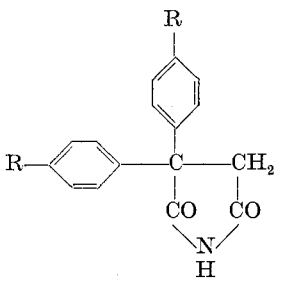
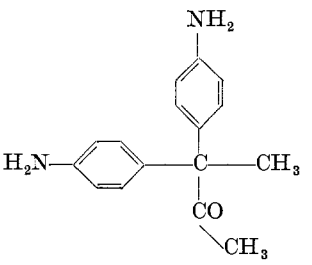
2,2-Diphenylsuccinimide (I; R = H) has been claimed to possess interesting biological activities.[1] We have prepared a number of



(I)



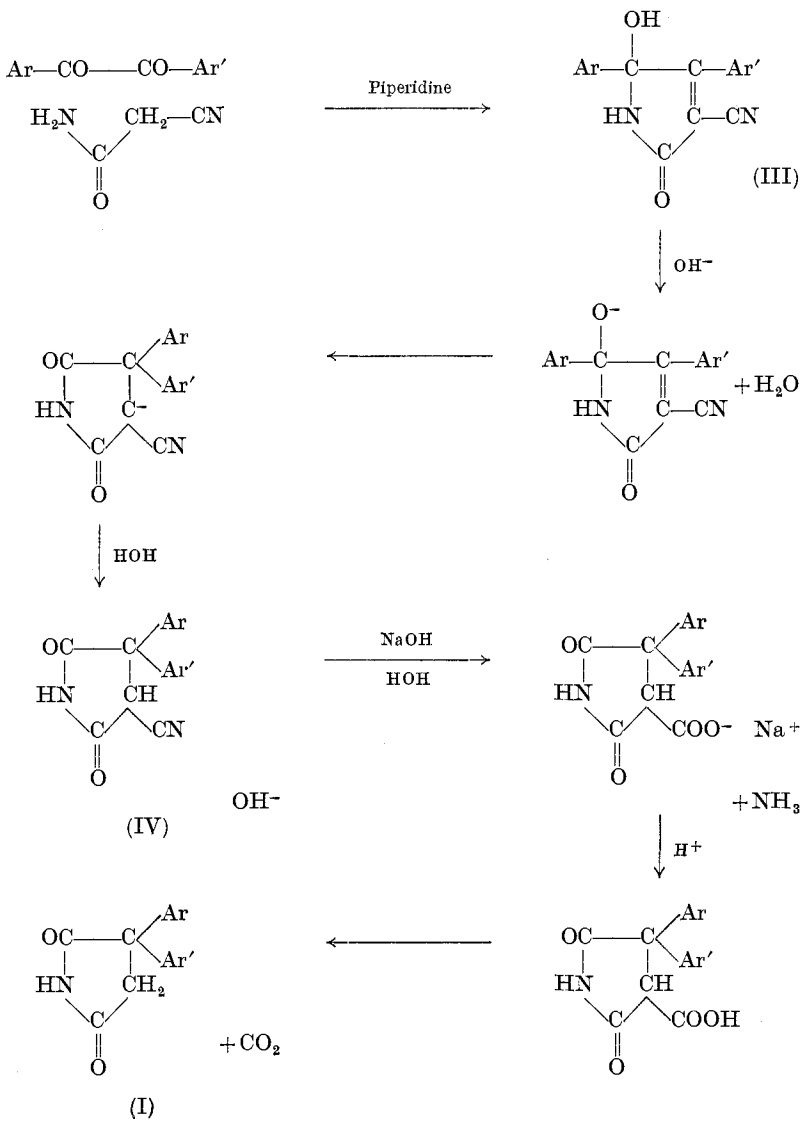
(II)

2,2-diaryl succinimides (I) in order to evaluate some of their pharmacological properties. Our main interest was to detect possible acute anticorticoid activity similar to that exhibited by Amphenone B (II) and its analogues.[2,3]

For the preparation of diaryl succinimides we employed the method of Queen which involved a novel type of rearrangement.[4] Diaryl 1,2-diketones were condensed with cyanoacetamide to form 4-cyano-2-hydroxy-5-oxo-2,3-diaryl-Δ^3-pyrrolines (III). Structure (III) was supported by the following spectral characteristics: an absorption band at 295 mμ (ϵ = 11,000, ethanol) for this type of conjugation and a band at 1710 cm^{-1} (Nujol mull) for the cyclic amide carbonyl group. Furthermore, the correctness of the structure (III) was proven by alternative synthesis.[5]

In boiling aqueous alkaline solution, the pyrroline (III; Ar = Ar′ = phenyl) was reported to undergo a rearrangement accompanied by the loss of the nitrile group to yield diphenyl succinimide.[4] We were able to perform the series of these reactions stepwise. The use of sodium methoxide in ethanol induced the

rearrangement with retention of the nitrile group. The stable intermediates, the 2,2-diaryl-3-cyanosuccinimides (IV), have been isolated and characterized. Upon treatment with alkali in



aqueous solution, the intermediates (IV) were converted into β-ketocarboxylic acid derivatives, which on acidification underwent decarboxylation to give the desired diaryl succinimides.

Compounds (V–IX), as listed in Table I, exhibited a carbonyl absorption band in the range of 1710–1735 cm^{-1}, in some instances accompanied by a second weaker band at 1680–1700 cm^{-1}. The presence of the nitrile group was indicated by an absorption peak in the region of 2240–2265 cm^{-1}.

The diarylsuccinimides, Table II, showed a medium to weak absorption band between 1770 and 1795 cm^{-1} and a strong band at 1712–1730 cm^{-1}. Succinimide itself was reported to exhibit three amide carbonyl frequencies (cm^{-1}) in Nujol mull: 1786s, 1727(sh)s and 1715s broad.[6]

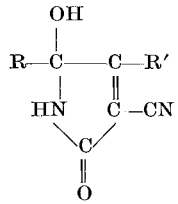
The intermediate compounds (X, XI and XIV), possessing structure IV, showed carbonyl absorption bands in the same region and pattern as the diarylsuccinimides indicating that the rearrangement had been completed. The nitrile frequencies of these intermediates were at 2270–2280 cm^{-1} which are, on average, 30 cm^{-1} higher than the nitrile bands of structure III. This hypsochromic shift is due to the loss of the double bond which was in conjugation with the nitrile group prior to the rearrangement.

The pyrroline type compounds, listed in Table I, did not exhibit any interesting pharmacological activity. Among the succinimides, as shown in Table II, our interest was focused on compounds XIII and XIX.

Compound (XIII) may be regarded as an Amphenone analogue in which the aliphatic chain had been modified and ring-closed. The adrenal cannulation test in the dog[3,7] showed that XIII appeared to possess a slight activity of a short duration (approx. 10 min). This order of activity was not considered significant enough to warrant further study. Similar experience was gained in the estrogen series when the aliphatic part of hexestrol was ring-closed. Mueller and May[8] synthesized 1,2-bis(*p*-hydroxyphenyl)-cyclohexane (cyclohexestrol), which was found to be only weakly active as an estrogen. Chronic tests were not performed with XIII.

Compounds XVII, XVIII and XIX were prepared in order to compare them with the DDD-type adrenolytic agents. One of

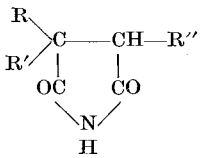
Table I. Pyrrolines



No.	R, R′[a]	Yield, %	m.p., °C	Formula	Calcd.			Found		
					C	H	N	C	H	N
V	α-pyridyl	50	201–203	$C_{15}H_{10}N_4O_2$	64·74	3·62	20·16	64·45	3·62	19·90
VI	6-methyl-α-pyridyl	52	215–217	$C_{17}H_{14}N_4O_2$	66·65	4·61	18·29	66·40	4·64	18·60
VII	*p*-chlorophenyl	79	239–240	$C_{17}H_{10}Cl_2N_2O_2$	59·15	2·92		59·14	2·94	
VIII	*o*-chlorophenyl	67	193–195	$C_{17}H_{10}Cl_2N_2O_2$	59·15	2·92	8·13	59·08	2·87	7·86
IX[a]	R: *o*-chlorophenyl R′: *p*-chlorophenyl	56	206–208	$C_{17}H_{10}Cl_2N_2O_2$	59·15	2·92		59·13	2·82	

[a] R and R′ are identical in each compound except IX.

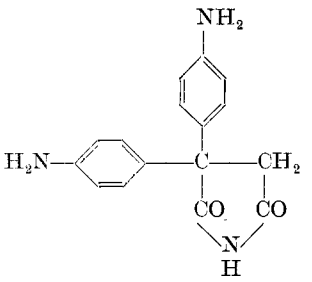
Table II. Succinimides



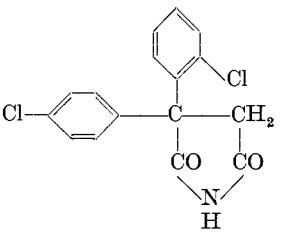
No.	R, R′[a]	R″	Yield, %	m.p., °C	Formula	Calcd.			Found		
						C	H	N	C	H	N
X	phenyl	CN	90	160–161	$C_{17}H_{12}N_2O_2$	73·90	4·38	10·14	73·88	4·45	10·22
XI[b]	phenyl	CN	68	149–151	$C_{18}H_{14}N_2O_2$	74·47	4·86	9·65	74·18	4·95	9·79
XII	*p*-nitrophenyl	H	30	270–273	$C_{16}H_{11}N_3O_6$	56·31	3·25	12·31	55·99	3·16	12·08
XIII	*p*-aminophenyl	H	32	224–228	$C_{16}H_{15}N_3O_2$	68·31	5·38	14·94	68·07	5·56	15·03
XIV	6-methyl-α-pyridyl	CN	66	210–211	$C_{17}H_{14}N_4O_2$	66·65	4·61	18·29	66·50	4·60	18·29
XV	6-methyl-α-pyridyl	H	29	168–170	$C_{16}H_{15}N_3O_2$	68·31	5·38	14·94	68·29	5·40	14·78
XVI	α-pyridyl	H	60	162–165	$C_{14}H_{11}N_3O_2$	66·39	4·38	16·59	66·39	4·44	16·52
XVII	*p*-chlorophenyl	H	39	148–151	$C_{16}H_{11}Cl_2NO_2$	60·02	3·46	4·38	60·27	3·49	4·54
XVIII	*o*-chlorophenyl	H	79	198–200	$C_{16}H_{11}Cl_2NO_2$	60·02	3·46	4·38	60·03	3·41	4·48
XIX*	R: *p*-chlorophenyl R′: *o*-chlorophenyl	H	31	218–221	$C_{16}H_{11}Cl_2NO_2$	60·02	3·46	4·38	60·29	3·49	4·50

[a] R and R′ are identical in each compound except XIX.

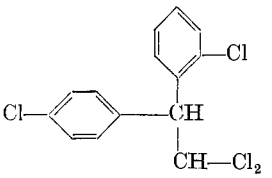
[b] XI possesses an *N*-methyl group.



(XIII)



(XIX)



(XXI) (*o,p'*-DDD)

the constituents of the technical insecticide Rothan* is *o,p'*-DDD (XXI).[9] This substance (XXI) was found to cause a much more pronounced adrenal cortical inhibition and a marked atrophy of this gland than the isomeric *p,p'*-DDD.[10,11] Neither *o,p'*-DDD (XXI), nor compounds XVII–XIX have shown any adrenal cortical inhibitory activity in the acute adrenal vein cannulation test. Compound XIX has also been tested by feeding 50 mg/kg of it in combination with sesame oil to a dog for three days. Under these conditions *o,p'*-DDD (XXI) exhibited a marked activity; however, compound XIX failed to do so.

In our experience the chronic type activity involving a diminished adrenal cortical hormone excretion accompanied with atrophy of the gland, such as displayed by *o,p'*-DDD and Perthane,[12] seems to be restricted to only a few chemical structures. On the other hand, the acute type of hormonal inhibition as caused by Amphenone[2] or SU-4885[13,14] may be encountered in a great number of compounds belonging to a wide variety of considerably differing chemical groups.[2]

* Rohm and Hass Co.

Experimental

4-Cyano-2-hydroxy-5-oxo-2,3-bis(α-pyridyl)-Δ³-pyrroline (V). Piperidine (5·5 g, 0·065 moles) was added dropwise to a stirred mixture of α-pyridil (11·0 g, 0·05 moles) and α-cyanoacetamide (4·25 g, 0·05 moles) in ethanol (175 ml). The resultant solution was refluxed for ½ h, whereupon the solvent was partially removed. A brown residue was obtained which was slurried in water, filtered and dried. Upon successive recrystallizations from ethanol and then from toluene, the pure product melted at 201–203°. The other pyrrolines (VI–IX) were prepared in a similar fashion.

2,2-Bis(α-pyridyl)-succinimide (XVI). The above compound (V) (3·1 g, 0·0112 mole) was refluxed for 2 h in 4 N sodium hydroxide (60 ml). The reaction mixture was chilled, acidified with 2 N hydrochloric acid until Congo blue reaction, and then evaporated to dryness. The dry solid was extracted several times with warm, absolute methanol. The combined extracts were neutralized with a methanolic solution of dry ammonia and again evaporated to dryness. The crude product weighed 1·7 g and melted at 140–150°. Recrystallization of this material from toluene and from hot water yielded pure product, m.p. 162–165°.

Compound (XV) was prepared in the same manner as above. In the case of the chlorophenyl succinimides (XVII–XIX), it was only necessary to neutralize the reaction mixture and extract the products with ether.

2,2-Diphenyl-3-cyanosuccinimide (X). 4-Cyano-2-hydroxy-5-oxo-2,3-diphenyl-Δ³-pyrroline (10·0 g, 0·032 mole) was refluxed for 2 h in ethanol (250 ml) containing sodium methoxide (41·0 g). After removal of the solvent under reduced pressure, the remaining solid was dissolved in water. The basic solution was neutralized with 6 N hydrochloric acid and extracted three times with ether. The combined extracts were washed with a saturated solution of sodium chloride and dried (Na_2SO_4 anhyd.). The gummy residue which was left after evaporation of the ether was recrystallized from ethanol–water to give the desired cyanosuccinimide (8·1 g) m.p. 160–161°.

N-*Methyl-2,2-diphenyl-3-cyanosuccinimide* (XI). 2,2-Diphenyl-3-cyanosuccinimide (1·3 g, 0·0047 mole) and an equivalent amount of sodium hydroxide (0·188 g) in acetone (3 ml) were combined

with dimethyl sulphate (0·296 g) in acetone (3 ml). The reaction mixture was refluxed for 1 h during which time it became neutral. The solvent was exchanged for water and the product was extracted three times with ether. The combined extracts yielded a viscous oil which upon addition of petroleum ether slowly crystallized. After recrystallization from ethanol and a mixture of ethanol and water the pure product melted at 149–151°.

2,2-Diphenylsuccinimide (I; R = H). 2,2-Diphenyl-3-cyanosuccinimide (4·1 g) was refluxed for 2 h with sodium hydroxide (14 g) in water (85 ml). The reaction mixture was cooled to room temperature and extracted twice with ether. The extracts were discarded and the basic aqueous layer was acidified with 6 N hydrochloric acid. The gummy precipitate was heated to boiling for a few minutes until evolution of carbon dioxide ceased. In one instance the carbon dioxide was passed through a clear barium hydroxide solution and barium carbonate was isolated. The acidic aqueous suspension was cooled to room temperature and the water decanted. The residue was taken up in ethanol and crystallized by the addition of water. The yield was 1·44 g (38·6 per cent), m.p. 142–143°. Upon admixture with a specimen prepared directly from pyrroline (III; Ar = Ar′ = Ph) by the action of sodium hydroxide[4] the melting point was undepressed.

2,2-Bis-(p-*nitrophenyl*)-*succinimide* (XII). A cold mixture of fuming nitric acid (12 ml, *d* 1·5) and acetic anhydride (12 ml) was added dropwise to a solution of 2,2-diphenylsuccinimide (2·8 g) in acetic anhydride (50 ml) with stirring, maintaining the temperature below 0°. The reaction mixture was kept cold overnight (−8°) and then poured into ice water. A small amount of ethyl acetate was added and the tan-coloured precipitate was collected on a sintered glass funnel. Upon drying in a desiccator the crude product melted at 237–246° and weighed 1·16 g. After recrystallization several times from a mixture of dioxan and water the pure compound melted at 270–273°.

2,2-Bis-(p-*aminophenyl*)-*succinimide* (XIII). The above dinitro compound (2·5 g, 0·073 moles) was dissolved in dioxan and hydrogenated at room temperature and atmospheric pressure over a catalyst (1·0 g) of palladium (5 per cent) on charcoal. The absorption of the calculated amount of hydrogen was complete in 5 h. The catalyst was filtered off and the gummy residue

was dissolved in 2 N hydrochloric acid. Upon neutralization with 2 N sodium hydroxide the product precipitated. By recrystallization from ethanol–water and ethyl acetate–pentane the pure compound melted at 224–228°.

Summary. Benzil type diketones have been condensed with α-cyanoacetamide to yield substituted pyrrolinones, which in turn have been rearranged in basic medium. Rearrangement in ethanol with sodium methoxide produced 2,2-diaryl-3-cyanosuccinimides, whereas the use of sodium hydroxide in water led to 2,2-diarylsuccinimides.

The intermediate pyrrolines (V–IX) did not exhibit any significant biological activity. The succinimides (X–XIX) were tested in the dog for adrenal cortical inhibition. Only 2,2-bis-(*p*-aminophenyl)-succinimide (XIII) was found to possess weak Amphenone-like activity.

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References

[1] Chen, G., Portman, R., Ensor, C. R. and Bratton, A. C. *J. Pharmacol.* **103**, 54 (1951)
[2] Bencze, W. L. and Allen, M. J. This Journal, **1**, 395 (1959)
[3] Chart, J. J. and Sheppard, M. This Journal, **1**, 407 (1959)
[4] Queen, A. *Chem. & Ind. (Rev.)*, 196 (1958)
[5] Jocelyn, P. C. and Queen, A. *J. chem. Soc.*, 4437 (1957)
[6] Abramovitch, R. A. *J. chem. Soc.*, 1413 (1957)
[7] Hume, D. M. and Nelson, D. H. In *Surgical Forum*, (40th) Clin. Congress of American College of Surgeons, 1954, p. 568. 1955. Philadelphia; Saunders
[8] Mueller, G. R. and May, R. J. *J. Amer. chem. Soc.*, **71**, 3313 (1949)
[9] Haller, H. L., Bartlett, P. D., Drake, N. L., Newman, M. S., Cristol, S. J., Eaker, C. M., Hayes, R. A., Kilmer, G. W., Magerlein, B., Mueller, G. P., Schneider, A. and Wheatley, W. *J. Amer. chem. Soc.*, **67**, 1591 (1945)
[10] Cueto, C. and Brown, J. H. *Endocrinology*, **62**, 335 (1958)
[11] Vilar, O. and Tullner, W. W. *Endocrinology*, **65**, 80 (1959)
[12] Talliaferro, I. and Leone, L. *New Engl. J. Med.*, **257**, 855 (1957)
[13] Chart, J. J., Sheppard, H., Allen, M. J., Bencze, W. L. and Gaunt, R. *Experientia*, **14**, 151 (1958)
[14] Bencze, W. L. and Allen, M. J. *J. Amer. chem. Soc.*, **81**, 4015 (1959)