81. *The Reaction between Diphenylamine and Malonic Esters.*

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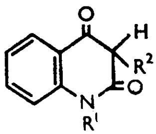
Diphenylamine with two mols. of malonic ester gives a product now shown to be the tricyclic amide (IIA; R = Ph); reaction with monoalkylmalonic esters, however, gave the expected 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxoquinolines (I).

BAUMGARTEN and RIEDEL[1] reported that diphenylamine condenses with boiling diethyl malonate with evolution of ethanol to give a high-melting solid formulated by them as 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline (I; R^1 = Ph; R^2 = H). In our hands this reaction gave a product (II) of very similar physical properties to that obtained by these authors, but elemental analyses and molecular-weight determinations were consistent only with the formula $C_{18}H_{11}O_4N$, suggesting that, in fact, the base had reacted with two mols. of ester in the following manner:

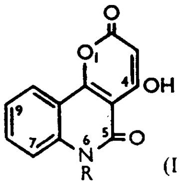
$$Ph_2NH + 2CH_2(CO_2Et)_2 \longrightarrow C_{18}H_{11}O_4N + 4EtOH$$

A similar product was obtained from *N*-methylaniline.

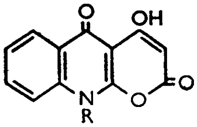
On general considerations the structures (IIA or IIB; R = Me or Ph) appeared most likely to represent these compounds and evidence is adduced to support this conclusion.



(I)



(IIA)



(IIB)

The infrared absorption spectrum of (II) showed strong bands at 1747, 1686, and 1572 cm.$^{-1}$ (in chloroform) consistent with the presence of a lactone carbonyl, cyclic amide carbonyl, and enolisable diketone system, respectively. The presence of the last group was confirmed by potentiometric titration (pK_a 8·64 in 85% dimethylformamide), and 1·2 active hydrogens were found by the Zerewitinov reaction. When heated with aqueous sodium hydroxide, the compound (II) was hydrolysed with concomitant loss of carbon dioxide to a compound $C_{17}H_{13}O_3N$ (III) in which the enolisable diketone system was still

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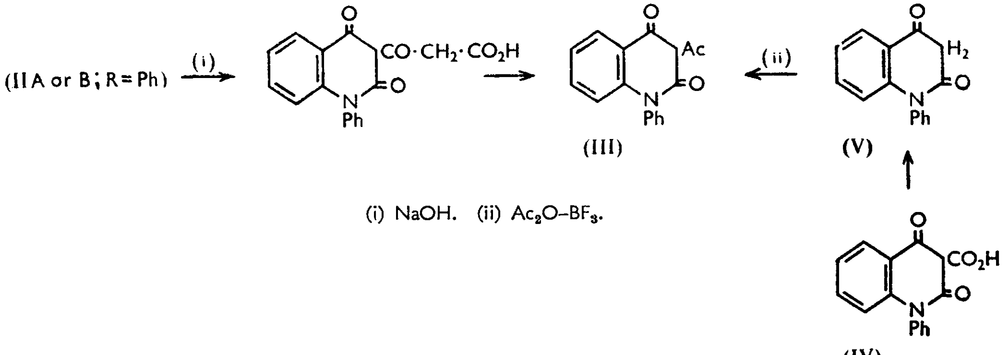
[1] Baumgarten and Riedel, *Ber.*, 1942, **75**, *B*, 984.

present (pK_a 9·26, and strong band at 1550 cm.$^{-1}$) but in which the ester group was no longer present as indicated by disappearance of the lactone-carbonyl band. Oxidation of this diketone with aqueous potassium permanganate gave a monocarboxylic acid $C_{16}H_{11}O_4N$ (IV) which lost carbon dioxide at its melting point to give 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline (V), identical in all respects with an authentic specimen prepared from acetic anhydride and diphenylamine.[2] These reactions, outlined above, are consistent with the formulation of the starting material as either (IIA) or (IIB).



(III)

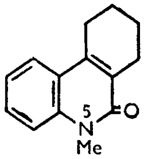
(V)

(IV)

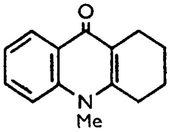
(i) NaOH. (ii) Ac_2O–BF_3.

Confirmatory evidence for the structure of the diketo-amide (III) was obtained by its resynthesis from (V) and acetic anhydride in the presence of boron trifluoride, a method which appears to be specific for the *C*-acylation of diketones.[3] Attempts to differentiate between the alternatives (IIA and IIB) by ozonolysis in acetic acid or carbon tetrachloride proved unfruitful, the sole product being the monocarboxylic acid (IV), due presumably to the enolisation of the β-diketone system in solution; a decision was therefore sought from spectral evidence.

The infrared spectra of α-quinolones and other six-membered heterocyclic amides are reported[4-6] to show strong carbonyl absorption bands in the 1680—1650 cm.$^{-1}$ region whereas γ-quinolones absorb strongly in the 1630—1620 cm.$^{-1}$ region. These differences also held in two model compounds containing a third ring, *e.g.*, (VI) and (VII), which had carbonyl bands at 1650 cm.$^{-1}$ and 1626 cm.$^{-1}$, respectively. It therefore appears that the 1686 cm.$^{-1}$ band in the spectrum of (II) favours an α- rather than a γ-quinolone structure. Furthermore, in the ultraviolet region, α-quinolones show a strong absorption peak at 320 mμ whereas γ-quinolones have a characteristic bifurcated band in the 320—360 mμ region,[5,6,8,9] the latter characteristic being found in the spectrum of (VII).



(VI)



(VII)

When allowance is made for the extra chromophore in (IIA) or (IIB) the ultraviolet

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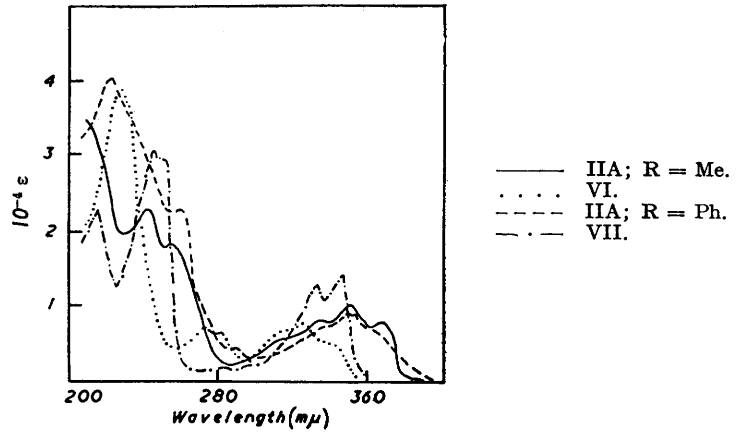
[2] B.P. 623,323.
[3] Rogers and Herchel Smith, *J.*, 1955, 341.
[4] Witcop, Patrick, and Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2641.
[5] Grundon, McCorkindale, and Roger, *J.*, 1955, 4284.
[6] Edwards and Singh, *Canad. J. Chem.*, 1954, **32**, 687.
[7] Reed, *J.*, 1944, 425.
[8] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[9] Steck, Ewing, and Nachod, *ibid.*, 1949, **71**, 238.

absorption curve of (II) closely resembles those of α-quinolones and (VI) (Figure). Spectral evidence therefore fully supports the formulation of Baumgarten and Riedel's compound as (IIA) and formulæ of the derivatives described by them should be modified accordingly.

In contrast to the unsubstituted ester, monoalkylmalonic esters reacted equimolecularly with *N*-monosubstituted anilines to give 1 : 3-disubstituted 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxoquinolines (I); a series of these compounds, prepared for general pharmacological examination, is described in the Experimental section.



EXPERIMENTAL

Light petroleum refers to material of b. p. 40—60°. Infrared spectra are reported only for the 1750—1480 cm.$^{-1}$ region and, unless specified to the contrary, were obtained on " Nujol " mulls.

5 : *6-Dihydro-4-hydroxy-2 : 5-dioxo-6-phenyl-2*H*-pyrano*[3,2-c]*quinoline* (IIA; R = Ph).—Ethyl malonate (400 g.) and diphenylamine (169 g.) were heated for 6 hr. during which ethanol (152 ml.) was collected by distillation through a short Vigreux column. The cooled (100°) mixture was stirred into methanol (1 l.) and the orange crystals (189 g., 62%) were collected and well rinsed with methanol. Many crystallisations from xylene and dioxan were required to give the *lactone* as colourless needles, m. p. 296—297° [Found: C, 70·7; H, 3·7; N, 4·6%; *M* (isothermal distillation in dimethylformamide), 284, 295. $C_{18}H_{11}O_4N$ requires C, 70·8; H, 3·6; N, 4·6%; *M*, 305]; pK_a 8·64 (in 85% dimethylformamide); $\lambda_{max.}$ (in ethanol) 220, 258, 289, 338 sh., 350, 362 sh. mμ (ε 40,200, 23,300, 4500, 7700, 8900, 7100, respectively); $\nu_{max.}$ 1751, 1691 s, 1666, 1622 w, 1579, 1563, 1506 s, 1439 (Nujol mull), and 1747 s, 1686, 1627 w, 1607 w, 1572 s cm.$^{-1}$ (chloroform).

5 : *6-Dihydro-4-hydroxy-6-methyl-2 : 5-dioxo-2*H*-pyrano*[3,2-c]*quinoline* (IIA; R = Me).—Interaction of methylaniline and ethyl malonate under the same conditions as above furnished the lactone (99 g.; 41%) as a light brown powder. Crystallisation from dioxan and xylene gave the pure *product* as needles, m. p. 253—254° (Found: C, 64·0; H, 3·6; N, 5·6. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7; N, 5·8%); pK_a 8·30 (in 85% dimethylformamide); $\lambda_{max.}$ (in ethanol) 242, 254, 335 sh, 350, 366 mμ (ε 23,300, 18,500, 8000, 10,000, 8100); $\nu_{max.}$ 1750 s, 1683, 1626 w, 1587, 1554, 1511 w (Nujol mull), and 1747, 1692, 1626 w, 1583, 1558 cm.$^{-1}$ (chloroform).

Alkaline Hydrolysis of the Lactone (IIA; R = Ph).—A suspension of the lactone (27 g.) in 2N-sodium hydroxide (110 ml.) was refluxed for 2 hr. The resulting solution was cooled and acidified with 2N-hydrochloric acid to give the product as a voluminous white solid. Two crystallisations from methanol gave *3-acetyl-1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline* (III) (21·9 g., 86%) as microneedles, m. p. 234° (Found: C, 72·9; H, 4·6; N, 5·1. $C_{17}H_{13}ON$ requires C, 73·1; H, 4·7; N, 5·0%); pK_a 9·26 (in 85% dimethylformamide); $\nu_{max.}$ 1657 s, 1550 s, 1487 sh. cm.$^{-1}$.

A solution of boron trifluoride (4 g.) in acetic acid (10 ml.) was added to a suspension of

1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline[2] (5 g.) in acetic anhydride (50 ml.): heat was evolved and the solid dissolved. After 20 min. the mixture was poured into water (200 ml.) containing sodium acetate (10 g.), and the crude product collected. Crystallisation from methanol gave 3-acetyl-1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline (1·9 g.; 31%), m. p. 233—234° undepressed by admixture with an equal weight of the material (III) obtained as above.

Permanganate Oxidation of the Quinoline (III).—Saturated aqueous potassium permanganate was added with stirring to a solution of the quinoline (III) (5 g.) in 50% aqueous acetone (200 ml.) until a permanent pink colour was observed. After removal of manganese dioxide, the filtrate was acidified and the precipitate collected. Two crystallisations from methanol furnished 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline-3-carboxylic acid (IV) (1·2 g.) as pale yellow prisms, m. p. 187—189° (effervescence) with resolidification and melting at 295—298° (Found: C, 68·1; H, 4·0; N, 4·8%; equiv., 280. $C_{16}H_{11}O_4N$ requires C, 68·3; H, 3·9; N, 5·0%; equiv., 281); $\nu_{max.}$ 1687 s, 1622 s, 1598 w, 1574, and 1495 cm.$^{-1}$.

This acid (0·5 g.) was heated at 200° until effervescence ceased. Crystallisation of the residue from methanol gave 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline as needles, m. p. 297—298° (decomp.) undepressed by admixture with an authentic specimen[2]; $\nu_{max.}$ 1629 s, 1586, 1540 s, 1497 s cm.$^{-1}$.

Ozonolysis of the Lactone (IIA ; R = Ph).—A stream of ozone was passed through a suspension of finely powdered lactone (IIA; R = Ph) (1 g.) in acetic acid (25 ml.) for 3 hr. until a clear yellow solution was obtained. Zinc dust (3 g.) was then added with stirring and after 1 hr., the excess was filtered off. Dilution of the filtrate with water and crystallisation from aqueous acetic acid gave 1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxo-1-phenylquinoline-3-carboxylic acid identical in every respect with the material obtained previously.

7 : 8 : 9 : 10-*Tetrahydro-5-methylphenanthridone* (VI).—A solution of 7 : 8 : 9 : 10-tetrahydrophenanthridone[10] (0·5 g.) in acetone (20 ml.) containing anhydrous potassium carbonate (1 g.) and methyl iodide (2 g.) was refluxed for 2 hr. and then filtered. Evaporation of the filtrate yielded an oil which slowly crystallised. Crystallisation from light petroleum gave the *product* (0·3 g.) as leaflets, m. p. 63—64° (Found: C, 77·4; H, 7·4; N, 6·8. $C_{13}H_{15}O_4N$ requires C, 77·6; H, 7·5; N, 7·0%); $\nu_{max.}$ 1650 s, 1594 s, 1572 sh, 1503 sh (Nujol mull.), and 1653 s and 1608 cm.$^{-1}$ (carbon tetrachloride).

1 : 2 : 3 : 4-*Tetrahydro*-10-*methylacridone* (VII).—This material was prepared according to Reed's method.[7] It had infrared max. 1626, 1598, 1576 s, 1544 s (Nujol mull.), and 1626, 1607 s, 1579, and 1554 s cm.$^{-1}$ (chloroform).

1 : 3-*Dialkyl*-1 : 2 : 3 : 4-*tetrahydro*-2 : 4-*dioxoquinolines*.—A mixture of the *N*-alkylaniline (1 mol.) and monoalkylmalonic ester (1·3 mol.) was heated at the boiling point, ethanol of reaction being removed by fractionation through a Vigreux column. At the completion of the reaction, the mixture was cooled and the resulting solid crystallised from the appropriate solvent. In this manner the 1 : 3-dialkyl-1 : 2 : 3 : 4-tetrahydro-2 : 4-dioxoquinolines (I) recorded in the table were prepared

			Yield		Found (%)			Required (%)		
R^1	R^2	M. p.	(%)	Formula	C	H	N	C	H	N
Me	Ph	213—214°[1]	67	$C_{16}H_{13}O_2N$	76·4	5·1	5·5	76·5	5·2	5·6
Me	Bu	114—115[2]	48	$C_{14}H_{17}O_2N$	72·5	7·2	5·1	72·7	7·4	6·1
$CH_2{\cdot}CH{:}CH_2$	H	234—235[2]	16·5	$C_{12}H_{11}O_2N$	71·7	5·3	6·9	71·6	5·5	7·0
$CH_2{\cdot}CH{:}CH_2$	Bu	110—111[3]	80	$C_{16}H_{19}O_2N$	74·6	7·3	5·5	74·7	7·4	5·4
$CH_2{\cdot}CH{:}CH_2$	Ph	166—167[1]	35	$C_{18}H_{15}O_2N$	77·8	5·3	5·0	78·0	5·5	5·1
Ph	Bu	206—207[4]	52	$C_{19}H_{19}O_2N$	77·9	6·3	4·8	77·8	6·5	4·8

[1] Needles from methanol. [2] Prisms from chloroform–light petroleum. [3] Plates from chloroform–light petroleum. [4] Needles from chloroform–light petroleum.

RESEARCH DEPT., PARKE, DAVIS & CO. LTD.,
STAINES ROAD, HOUNSLOW, MIDDX.

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[10] Blount, Perkin, and Plant, *J.*, 1929, 1986.