INVESTIGATION ON RIBOFLAVIN ANALOGS

V. Trifluoromethyl Derivatives of Dinitrodihydrophenazine*

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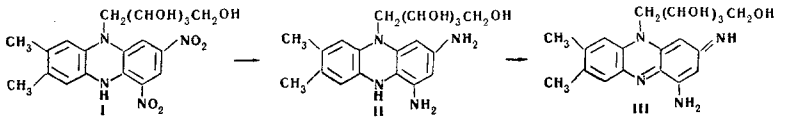
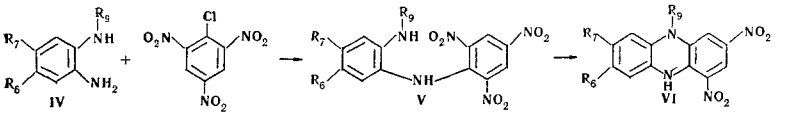
Dinitrotrifluoromethyl-d-galactyl- and β-hydroxyethyldihydrophenazines have been obtained for biological tests by the reaction of primary-secondary o-phenylenediamines with picryl chloride.

In a preceding communication the synthesis of trifluoromethyl derivatives of isoalloxazine, obtained as potential riboflavin antagonists, was described [1]. The investigations of Wolley [2] and of Sarett [3] have shown that 2,4-diamino-6,7-dimethyl-9-ribityl-9,10-dihydrophenazine (II) and 6,7-dimethyl-2,4-dinitro-9-ribityl-9,10-dihydrophenazine (I), which are structural analogs of the flavin, exhibit antivitamin activity (the first in vitro and in vivo and the second only in vivo). In all probability I is converted in the organism into II and then into the 4-amino-2-imino-2,9-dihydrophenazine III.



The latter, because of the distortion of the catalytic quinoid system, may act as a riboflavin competitor in cell respiration processes. In the present work, besides the replacement of the isoalloxazine nucleus by the dinitrodihydrophenazine nucleus used in compound I, a trifluoromethyl group has been introduced in place of one methyl group, and a β-hydroxyethyl or a 1'-d-galactyl group has been introduced in place of the 9-(1'-d-ribityl) group. This method of modification was undertaken in order to elucidate the influence of substituents in positions 6, 7, and 9 on biological activity, and also to compare the biological activity of the compounds obtained and the isoalloxazine derivatives of similar structure described in the preceding communication.

The synthesis of the compounds of general formula VI was carried out by the following route:



The o-phenylenediamines IV were obtained from the corresponding substituted o-nitroanilines by catalytic hydrogenation in ethanol. The compounds IV were not identified and were used directly for the reaction with picryl chloride. 2-(β-Hydroxyethyl)amino- and 2-(1'-d-galactyl) amino-2',4',6'-trinitrodiphenylamines (Va–Vf) are orange crystalline substances (properties in Table 1).

Table 1. Trinitrodiphenylamine Derivatives

Compound	R_9	R_7	R_6	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
Va	CH_2CH_2OH	CH_3	CF_3	174	$C_{16}H_{14}F_3N_5O_7$	43.12	3.27	15.77	43.15	3.15	15.70	69
Vb	CH_2CH_2OH	H	CF_3	176	$C_{15}H_{12}F_3N_5O_7$	41.86	2.73	16.69	41.76	2.78	16.25	83
Vc	CH_2CH_2OH	CF_3	H	168	$C_{15}H_{12}F_3N_5O_7$	41.37	3.08	16.23	41.76	2.78	16.25	54

*For part IV, see [1].

When compounds V were heated in ethanol with anhydrous sodium acetate, the closure of the dihydrophenazine ring took place. In contrast to the 2-(β-hydroxyethylamino)diphenylamines (Va–Vc), the conversion of 2-[(1'-d-galactyl)amino]-4-methyl-2',4',6'-trinitro-5-trifluoromethyldiphenylamine (Vd), 2-[(1'-d-galactyl)amino]-2',4',6'-trinito-4-trifluoromethyldiphenylamine (Ve), and 2-[(1'-d-galactyl)amino]-2',4,6'-trinitro-4-trifluoromethyldiphenylamine (Vf) into the corresponding dihydrophenazines took place even during their recrystallization from ethanol. Consequently, compounds Vd-f were not obtained in the analytically pure state. The dinitrodihydrophenazines obtained were colored (λ_{max} 550-555 nm) crystalline substances readily soluble in ethyl acetate and ethanol and sparingly soluble in water. Their constants are given in Table 2.

Table 2. Dinitrodihydrophenazine Derivatives

Compound	R_9	R_7	R_8	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
						C	H	N	C	H	N	
VIa	CH_2CH_2OH	CH_3	CF_3	270	$C_{16}H_{13}F_3N_4O_5$	48.18	3.38	14.03	48.12	3.23	14.00	67
VIb	CH_2CH_2OH	H	CF_3	273	$C_{15}H_{11}F_3N_4O_5$	46.72	2.82	15.07	46.87	2.87	14.55	68
VIc	CH_2CH_2OH	CF_3	H	248	$C_{15}H_{11}F_3N_4O_5$	46.76	2.80	14.68	46.87	2.87	14.55	58
VId	d-galactyl	CH_3	CF_3	235	$C_{20}H_{21}F_3N_4O_9$	46.35	4.19	10.65	46.33	4.05	10.81	74
VIe	d-galactyl	H	CF_3	237	$C_{19}H_{19}F_3N_4O_9$	45.48	3.65	11.28	45.24	3.78	11.11	69
VIf	d-galactyl	CF_3	H	228	$C_{19}H_{19}F_3N_4O_9 \cdot H_2O$	43.78 43.54	3.85 3.95	10.62	43.68	4.02	10.72	52

EXPERIMENTAL

Reduction of the substituted nitroanilines. Raney nickel (0.5 g) was added to a suspension of 0.00175 mole of an o-nitroaniline in 8 ml of ethanol and hydrogen was passed through at atmospheric pressure and room temperature for 12–15 hr. The catalyst was filtered off and washed with 2–3 ml of ethanol. The ethanolic solution was used for condensation with picryl chloride.

Reaction of the substituted o-phenylenediamines with picryl chloride. To 0.00175 mole of o-phenylenediamine in 10 ml of ethanol was added 0.0035 mole of anhydrous sodium acetate in 10 ml of H_2O, and this was followed slowly by 0.0018 mole of picryl chloride in 14 ml of ethanol. The reaction mixture was shaken for 1 hr and was left to stand in the refrigerator for several hours. The crystalline precipitate was filtered off, washed with 50% ethanol, and dried in vacuum. It was recrystallized from ethanol.

Closure of the dihydrophenazine ring. A solution of 0.0017 mole of the compound concerned and 0.0085 mole of anhydrous sodium acetate in 25 ml of ethanol was boiled for 5 hr and then it was cooled, and the residue was washed with ethanol, water, and ethanol again. It was crystallized from ethanol or ethyl acetate (VIf was crystallized from 70% ethanol).

REFERENCES

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